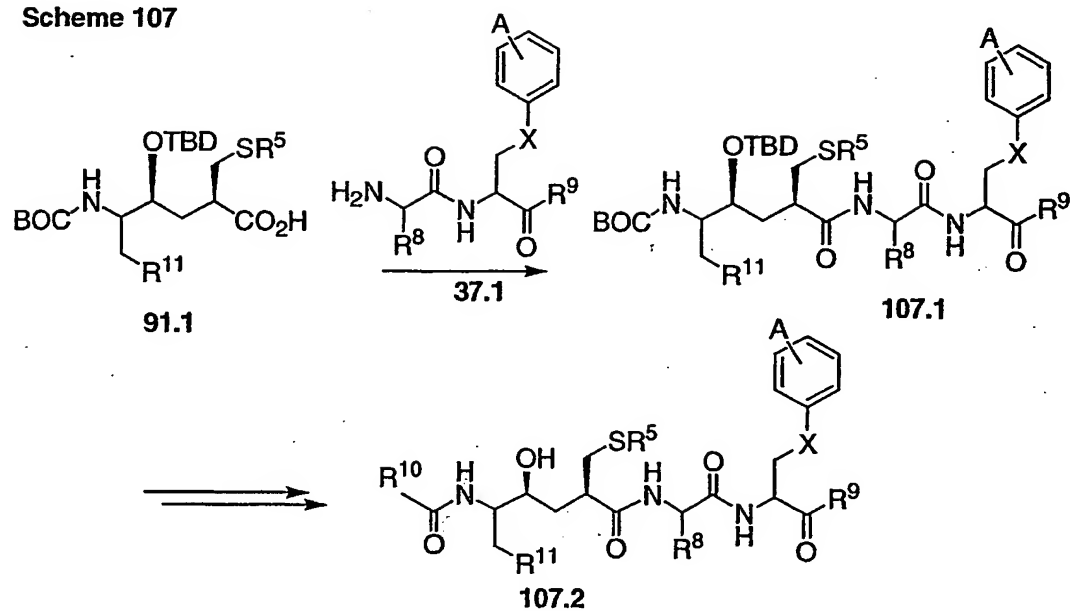
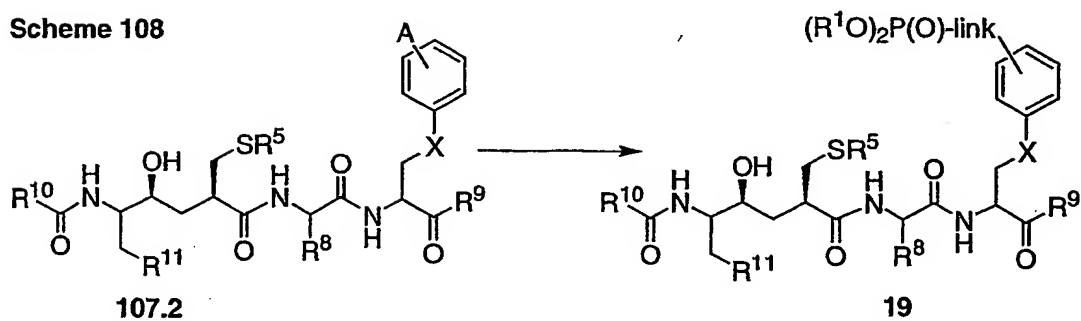


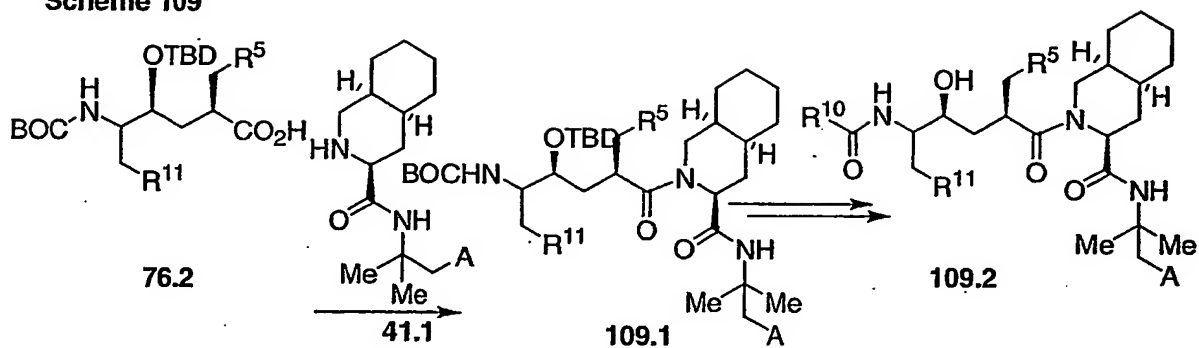
Scheme 107



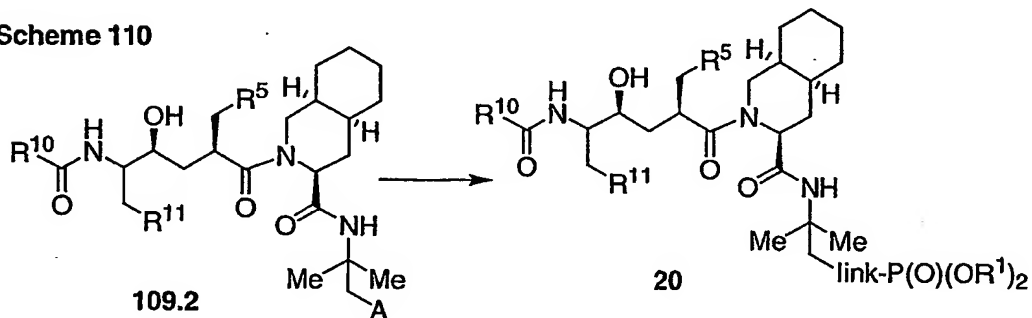
Scheme 108



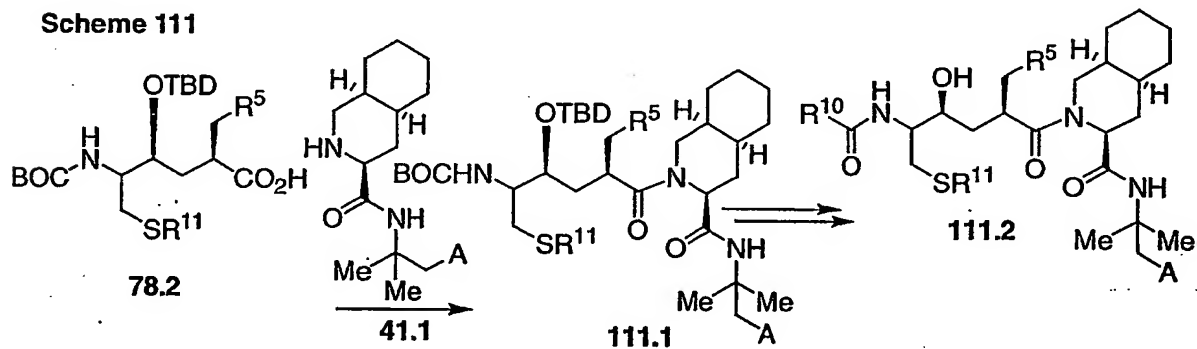
Scheme 109



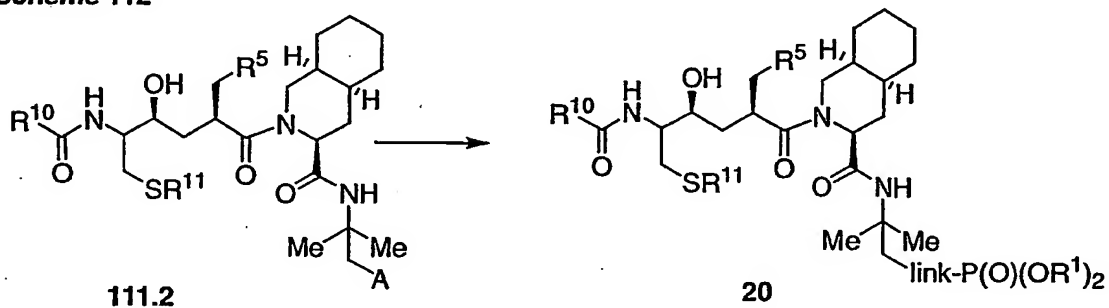
Scheme 110



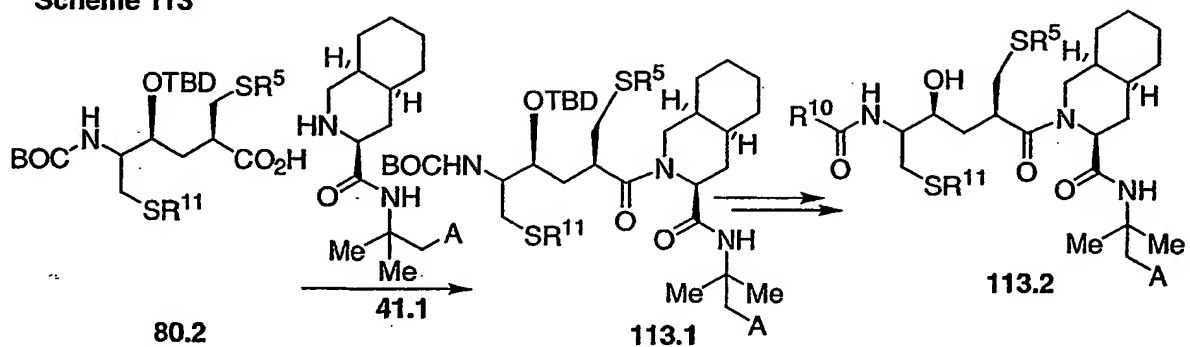
Scheme 111



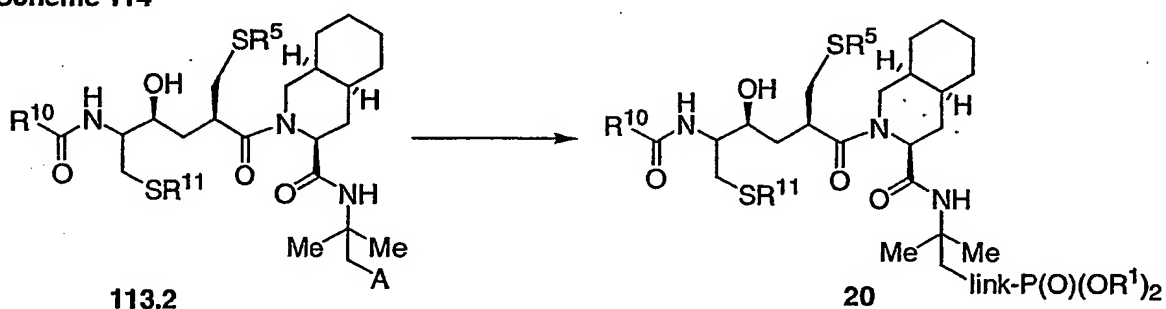
Scheme 112



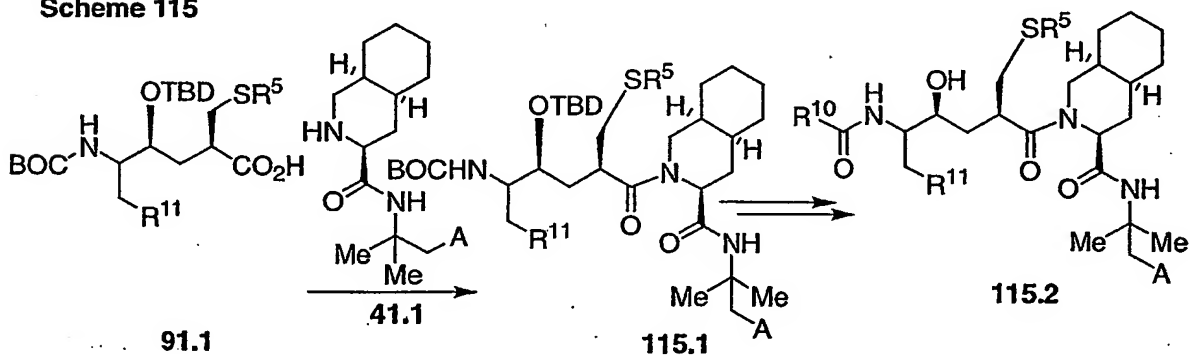
Scheme 113



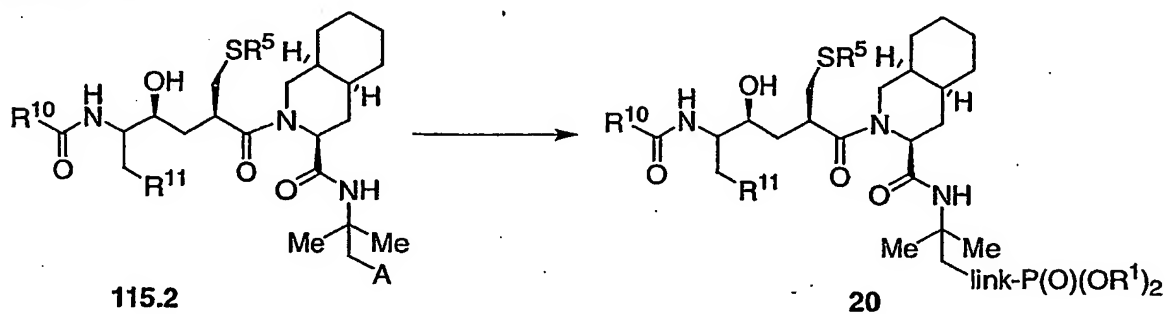
Scheme 114



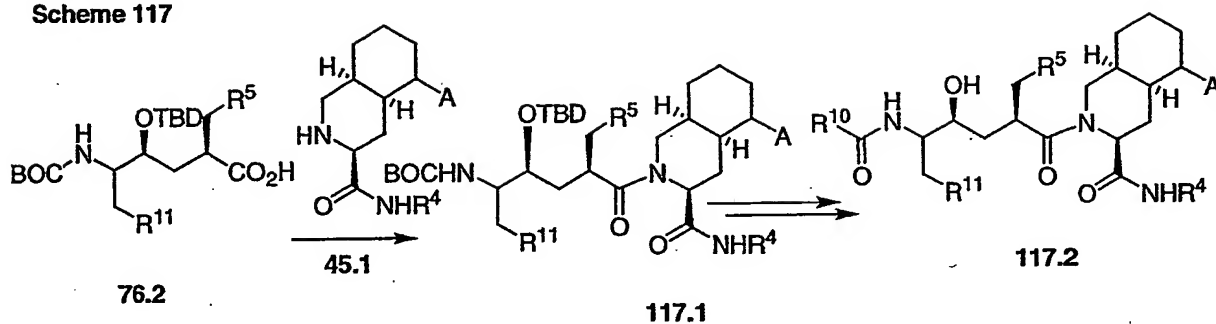
Scheme 115



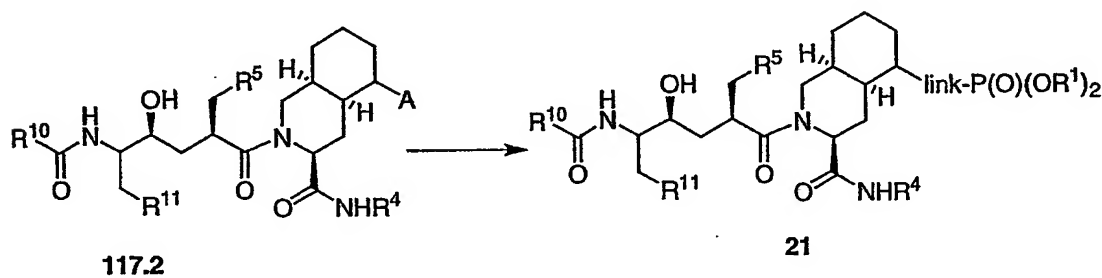
Scheme 116



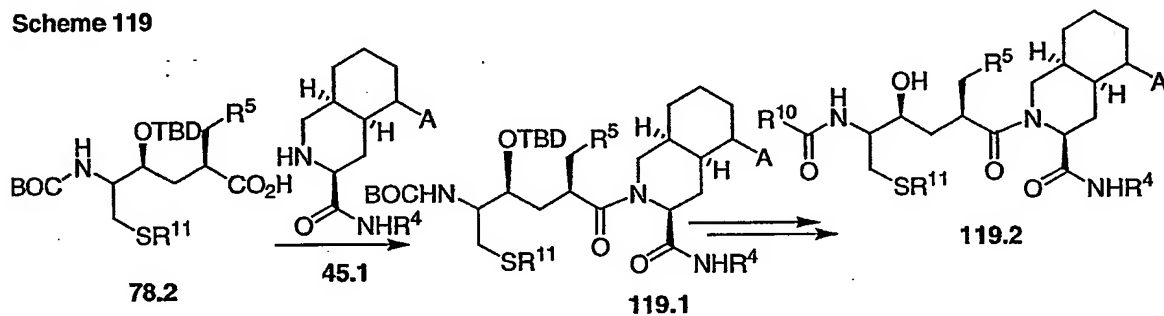
Scheme 117



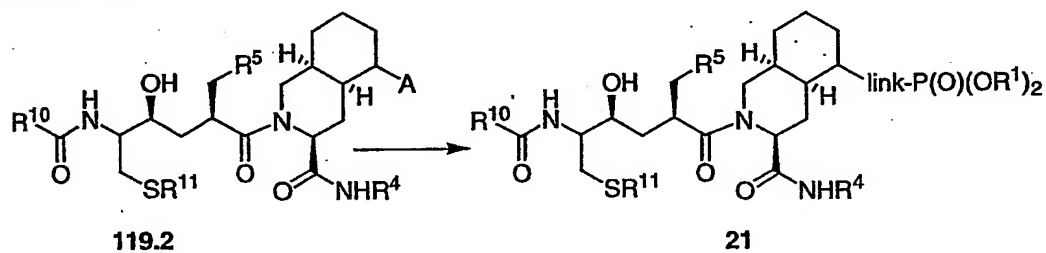
Scheme 118



Scheme 119



Scheme 120



Preparation of the phosphonate ester intermediates 21 in which X and X' are sulfur.

- 5 Schemes 121 and 122 illustrate the preparation of the phosphonate esters 21 in which X and X' are sulfur. As shown in Scheme 121, the carboxylic acid 80.2 is coupled with the amine

45.1 to give the amide 121.1. The product is then transformed, as described in Scheme 49, into the diamide 121.2.

The reactions shown in Scheme 121 illustrate the preparation of the compounds 121.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 122 depicts the conversion of the compounds 121.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X and X' are sulfur. In this procedure, the compounds 121.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

10 Preparation of the phosphonate ester intermediates 21 in which X is sulfur and X' is a direct bond.

Schemes 123 and 124 illustrate the preparation of the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 1, with the amine 45.1 to afford the amide 123.1. The product is then converted, as described in Scheme 49, into the diamide 123.2.

The reactions shown in Schemes 123 illustrate the preparation of the compounds 123.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br. Scheme 124 depicts the conversion of the compounds 123.2 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 21 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 123.2 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 21.

Preparation of the phosphonate ester intermediates 22 in which X and X' are direct bonds.

25 Schemes 125 and 126 illustrate the preparation of the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the carboxylic acid 76.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 125.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 125.2. The latter compound is then

coupled with the carboxylic acid 125.3 to produce the amide 125.4. The preparation of the carboxylic acid reactant 125.3 is described in Scheme 191.

The reactions shown in Scheme 125 illustrate the preparation of the compounds 125.4 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 126 depicts the conversion of the compounds 125.4 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X and X' are direct bonds. In this procedure, the compounds 125.4 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22

10 Preparation of the phosphonate ester intermediates 22 in which X is a direct bond and X' is sulfur.

Schemes 127 and 128 illustrate the preparation of the phosphonate esters 22 in which X is a direct bond and X' is sulfur. In this procedure, the carboxylic acid 78.2 is coupled, as described in Scheme 5 with the amine 1.6, to afford the amide 127.1. The BOC protecting group is then removed, as described in Scheme 49, to yield the amine 127.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 127.3.

The reactions shown in Scheme 127 illustrate the preparation of the compounds 127.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br. Scheme 128 depicts the conversion of the compounds 127.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X is a direct bond and X' is sulfur. In this procedure, the compounds 127.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

25 Preparation of the phosphonate ester intermediates 22 in which X and X' are sulfur.

Schemes 129 and 130 illustrate the preparation of the phosphonate esters 22 in which X and X' are sulfur. As shown in Scheme 129, the carboxylic acid 80.2 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 129.1. The BOC protecting group is then

removed, as described in Scheme 49, to yield the amine 129.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 129.3.

The reactions shown in Scheme 129 illustrate the preparation of the compounds 129.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],

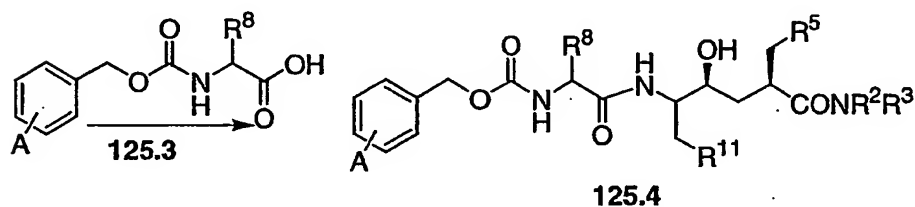
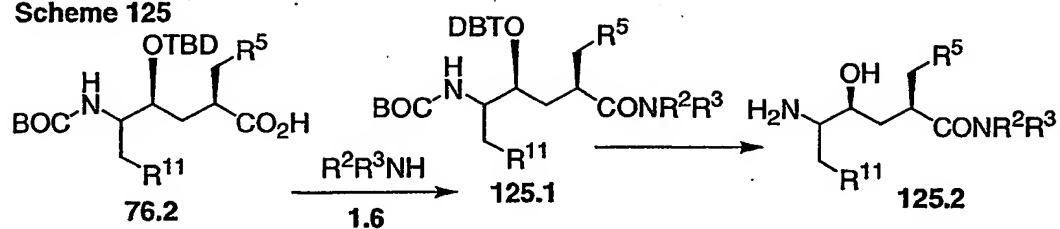
- 5 [SH], [NH], Br. Scheme 130 depicts the conversion of the compounds 129.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22, in which X and X' are sulfur. In this procedure, the compounds 129.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

- 10 **Preparation of the phosphonate ester intermediates 22 in which X is sulfur and X' is a direct bond.**

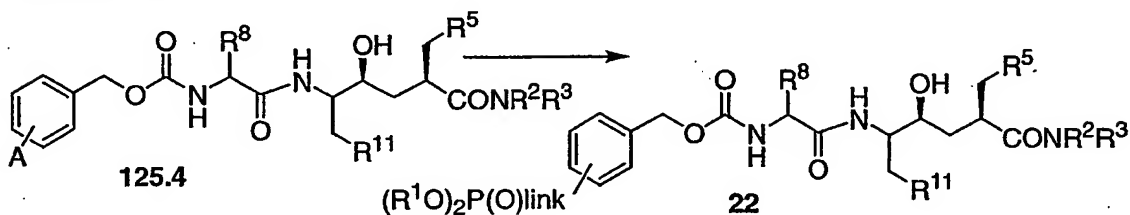
- Schemes 131 and 132 illustrate the preparation of the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the carboxylic acid 91.1 is coupled, as described in Scheme 5, with the amine 1.6, to afford the amide 131.1. The BOC protecting
15 group is then removed, as described in Scheme 49, to yield the amine 131.2. The latter compound is then coupled, as described in Scheme 1, with the carboxylic acid 125.3 to produce the amide 131.3.

- The reactions shown in Scheme 131 illustrate the preparation of the compounds 131.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH],
20 [SH], [NH], Br. Scheme 132 depicts the conversion of the compounds 131.3 in which A is [OH], [SH], [NH], Br, into the phosphonate esters 22 in which X is sulfur and X' is a direct bond. In this procedure, the compounds 131.3 are converted, using the procedures described below, Schemes 133 - 197, into the compounds 22.

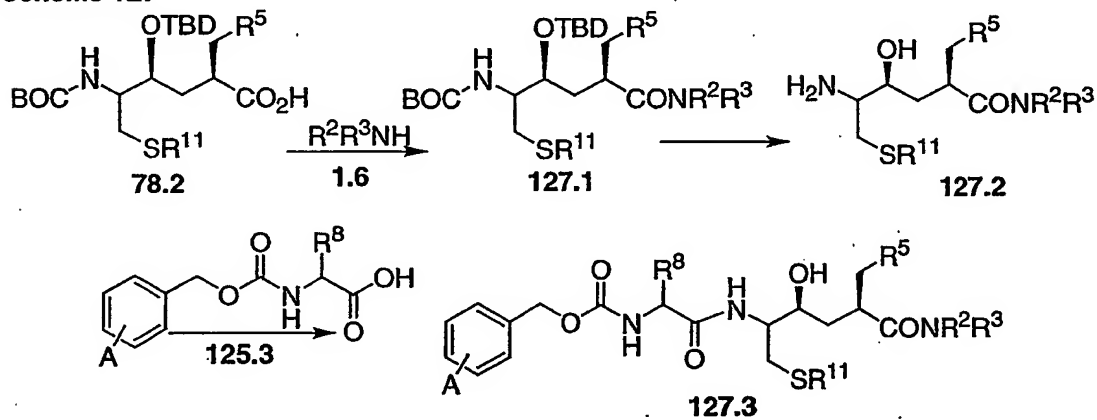
Scheme 125



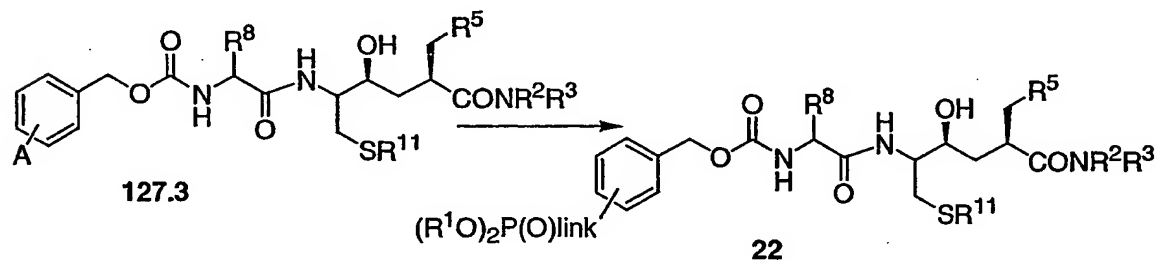
Scheme 126



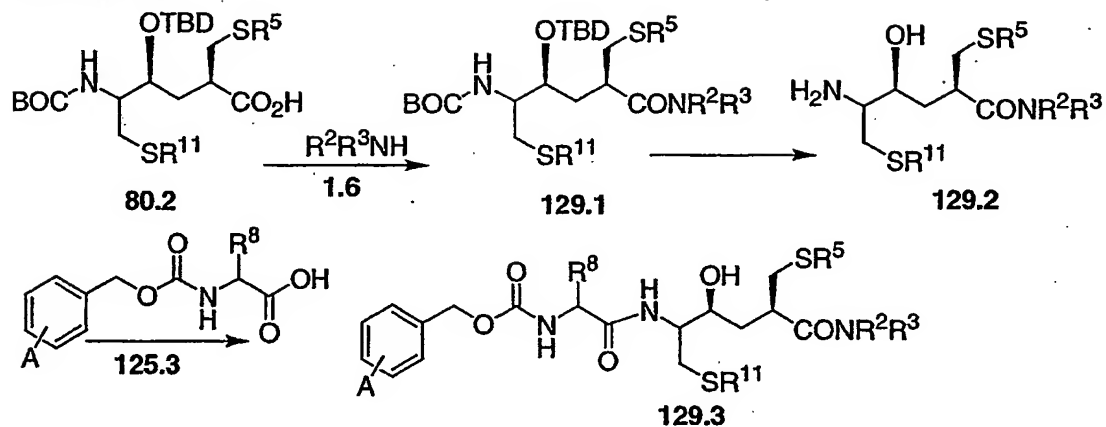
Scheme 127



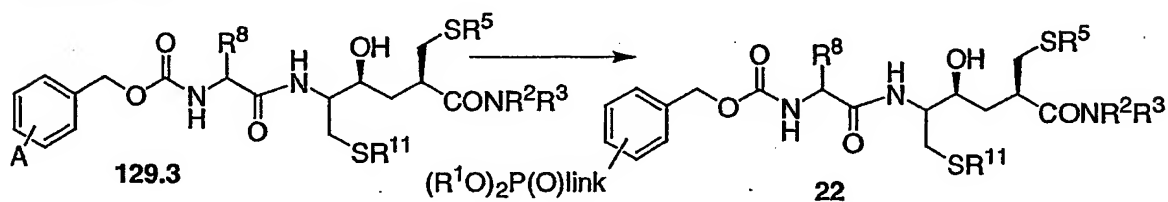
Scheme 128



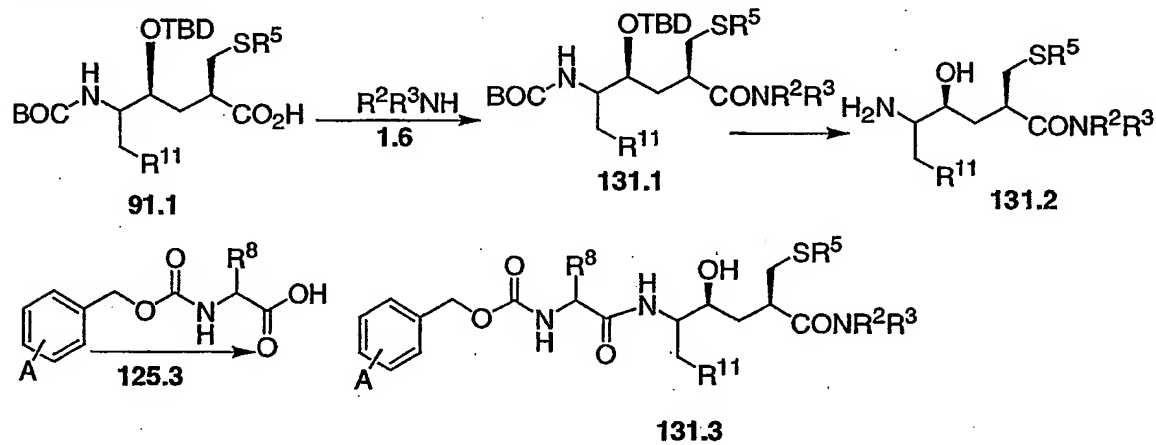
Scheme 129



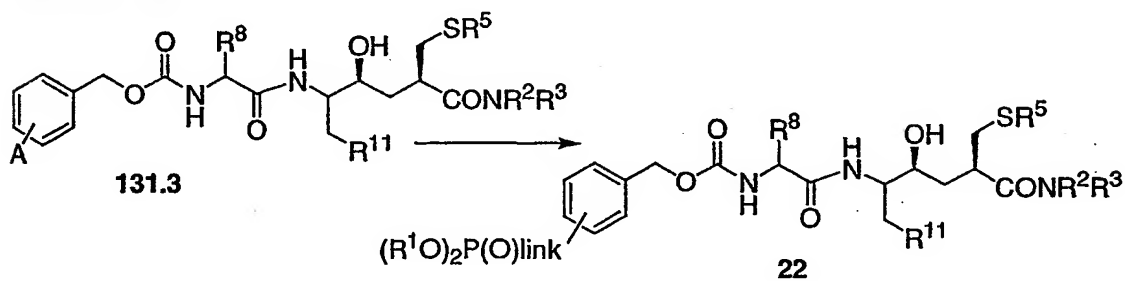
Scheme 130



Scheme 131



Scheme 132



Preparation of aminoindanol derivatives 1.2 incorporating phosphonate moieties.

Scheme 133 illustrates the preparation of variously substituted derivatives of 3-amino-indan-1,2-diol, the preparation of which is described in J. Med. Chem., 1991, 34, 1228. The
5 alcohols, thiols, amines and bromo compounds shown in Scheme 133 can then be transformed into phosphonate-containing reactants 1.2, as described below, (Schemes 134 - 137). The reactants 1.2 are employed in the preparation of the phosphonate esters 1 and 16.

In order to effect changes to the 1-substituent, the starting material 133.1 is transformed into the protected compound 133.2. For example, the aminoalcohol 133.1 is treated with 2-
10 methoxypropene in the presence of an acid catalyst, such as p-toluenesulfonic acid, in a solvent such as tetrahydrofuran, as described in WO9628439, to afford the acetonide-protected product 133.2.

The amino group present in 133.2 is protected to afford the intermediate 133.3, in which R¹² is a protecting group, stable to the subsequent reactions. For example, R¹² can be
15 carbobenzyloxy (cbz), tert-butoxycarbonyl (BOC) and the like, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309.

The free hydroxyl group present in the N-protected acetonide 133.3 is then converted into a suitable leaving group, such as, for example, trifluoromethylsulfonyloxy, p-toluenesulfonyloxy
20 or, preferably, methanesulfonyloxy. This transformation is effected by treatment of 133.3 with a slight molar excess of the corresponding acid chloride or anhydride, in the presence of an organic base.

For example, treatment of 133.3 with methanesulfonyl chloride and pyridine in dichloromethane at ambient temperature affords the mesylate 133.4.

25 The α -mesylate group in the product 133.4 is then subjected to displacement reactions with nitrogen, sulfur or oxygen nucleophiles, to effect introduction of the various heteroatoms with inversion of stereochemistry.

For example, the mesylate 133.4 is reacted with a nitrogen nucleophile such as potassium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic
30 Transformations, by R. C. Larock, VCH, p. 399, to afford the amine 133.9.

Preferably, the mesylate 133.4 is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 133.5, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the β -amine 133.9.

5 The mesylate 133.4 is treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate group, followed by mild basic hydrolysis, for example by treatment with aqueous sodium bicarbonate or aqueous ammonia, to afford the β -thiol 133.12.

10 Preferably, the mesylate 133.4 is reacted with one molar equivalent of potassium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate 133.8. The product then treated with a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the β -thiol 133.12.

15 The mesylate 133.4 is transformed into the β -carbinol 133.7, by treatment with an oxygen nucleophile. Conversion of sulfonate esters and related compounds to the corresponding carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 481. For example, the mesylate can be reacted with potassium superoxide, in the presence of a crown ether such as 18-crown-6, as described in Tet. Lett., 3183, 1975, to
20 afford the β -carbinol 133.7.

The carbinol 133.3 is also transformed into the β -bromo compound 133.6. Methods for the conversion of carbinols to bromo compounds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 356.

For example, the α -carbinol 133.3 is reacted with hexabromoethane and triphenylphosphine, in
25 an aprotic solvent such as ethyl acetate, as described in Syn., 139, 1983, to afford the β -bromo compound 133.6.

Using the above described procedures for the conversion of the α -carbinol 133.3 into the β -oriented amine 133.9, thiol 133.12 and bromo compound 133.6, the β -carbinol 133.7 is transformed into the α -oriented amine or thiol 133.11 or the bromo compound 133.10.

30

Schemes 134 - 137 illustrate the preparation of aminoindanol derivatives incorporating the group $\text{link-P(O)(OR}^1)_2$, derived from the intermediates whose syntheses are described above (Scheme 133).

- 5 Scheme 134 depicts the preparation of phosphonate esters linked to the aminoindanol nucleus by means of a carbon chain and a heteroatom O, S or N. In this procedure, the hetero-substituted indanol 134.1 is reacted with a bromoalkylphosphonate 134.2, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for
- 10 example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80°C to afford the displacement products 134.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, by removal of the group R^{12} ,
- 15 then affords the amine 134.4.
- For example, the β -thiol 133.12 is reacted with an equimolar amount of dialkyl 4-bromobutyl phosphonate 134.5, the preparation of which is described in Synthesis, 1999, 9, 909, in dimethylformamide containing excess potassium carbonate, at ca 60°C to afford the thioether phosphonate product 134.6. Deprotection then affords the amine 134.7.
- 20 Using the above procedures, but employing, in place of the thiol 133.12, different carbinols, thiols or amines 134.1, and/or different bromoalkylphosphonates 134.2, the corresponding products 134.4 are obtained.

- Scheme 135 illustrates the preparation of aminoindanol derivatives in which the phosphonate ester group is attached by means of a nitrogen atom and a carbon chain. In this method, the
- 25 aminoindanol 135.1 is reacted with a formyl-substituted phosphonate ester, utilizing a reductive amination procedure. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 135.1 and the aldehyde
- 30 component 135.2 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 135.3. Deprotection, by removal of the R^{12} group, then affords the amine 135.4.

For example, equimolar amounts of the amine 133.11 and a dialkylformylphosphonate 135.5, prepared as described in US 3784590, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the product 135.6 which is then deprotected to produce the amine 135.7.

- 5 Using the above procedures, but employing, in place of the α -amine 133.11, the β -amine 133.9, and/or different formyl-substituted phosphonates 135.2, the corresponding products 135.4 are obtained.

- 10 Scheme 136 depicts the preparation of aminoindanol phosphonates in which the phosphonate moiety is attached to the nucleus by means of a heteroatom and one carbon. In this procedure, a carbinol, thiol or amine 136.1 is reacted with a dialkyl trifluoromethylsulfonyloxy phosphonate 136.2, in the presence of a suitable base, to afford the alkylation product 136.3. Deprotection of the product 136.3 then yields the amine 136.4. The base required for this reaction between 136.1 and 136.2 depends on the nature of the heteroatom X. For example, if
- 15 X is N or S, an excess of inorganic base such as, for example, potassium carbonate, cesium carbonate or the like, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products 136.3. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide, sodium hydride or the like, is employed, in the
- 20 presence of a solvent such as tetrahydrofuran.

- For example, the α -carbinol 133.3 is reacted with one equivalent of lithium hexamethyl disilylazide in tetrahydrofuran, followed by addition of an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate 136.5, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product 136.6. Deprotection, by removal of the
- 25 R¹² group, then affords the amine 136.7.

Using the above procedures, but employing, in place of the α -carbinol 133.3, different carbinols, thiols or amines 136.1, and /or different dialkyl trifluoromethylsulfonyloxymethyl phosphonates 136.2, the corresponding products 136.4 are obtained.

- 30 Scheme 137 illustrates the preparation of aminoindanol phosphonate esters in which the phosphonate group is attached directly to the aminoindanol nucleus.

In this procedure, the bromoindanol derivative **137.1** is reacted with a sodium dialkyl phosphite, in a suitable aprotic polar solvent such as dimethyl formamide or N-methylpyrrolidinone. Displacement of the bromo substituent occurs to yield the phosphonate **137.3**. Deprotection, by removal of the R¹² group, then affords the amine **137.4**.

5 For example, equimolar amounts of the α -bromo compound **133.10** and the dialkyl sodium phosphite **137.2**, are dissolved in dimethylformamide and the mixture is heated at ca. 60°C, as described in J. Med. Chem., 35, 1371, 1992, to afford the β -phosphonate **137.5**.

Alternatively, the phosphonate compound **137.5** is obtained by means of an Arbuzov reaction between the bromo compound **133.10** and a trialkyl phosphite P(OR¹)₃. In this procedure, as
10 described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product **137.5**. Deprotection of the latter compound affords the amine **137.6**.

Using the above procedures, but employing, in place of the α -bromo compound **133.10**, the β -bromo compound **133.6**, and/or different phosphites **137.2**, the corresponding phosphonates
15 **137.4** are obtained.

Preparation of phenylpropionic acid intermediates 5.1 incorporating phosphonate moieties.

20 Phenylpropionic acid derivatives incorporating the substituent link-P(O)(OR¹)₂ are prepared by the reactions illustrated in Schemes **139-143**, using as starting materials variously substituted phenylpropionic acids. The phenylpropionic acid derivatives **5.1** are employed in the preparation of the phosphonate esters **2** in which X is a direct bond.

A number of the substituted phenylpropionic acids required for the reactions shown in
25 Schemes **139-143** are commercially available; in addition, the syntheses of variously substituted phenylpropionic acids have been reported. For those substituted phenylpropionic acids which are not commercially available, and whose syntheses have not been reported, a number of well-established synthetic routes are available. Representative methods for the synthesis of substituted phenylpropionic acids from commercially available starting materials
30 are shown in Scheme **138**.

For example, variously substituted benzaldehydes **138.1** are subjected to a Wittig reaction with carboethoxymethylenetriphenylphosphorane **138.2**, as described in Ylid Chemistry, by A. W.

Johnson, Academic Press, 1966, p. 132, to afford the corresponding cinnamate esters 138.3. Equimolar amounts of the reactants 138.1 and 138.2 are heated in an inert solvent such as dioxan or dimethylformamide, at ca 50°C, to afford the product 138.3. Reduction of the double bond in the product 138.3 then afford the saturated ester 138.6, (X =H) which upon

5 hydrolysis yields the phenylpropionic acid intermediate 138.10.

Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 6. Typical of the available reduction methods are catalytic hydrogenation, for example using palladium catalysts, as described in Hydrogenation Methods, by P. N. Rylander, Academic Press, New

10 York, 1985, hydroboration-protonolysis, as described in J. Am. Chem. Soc., 81, 4108, 1959, or diimide reduction, as described in J. Org. Chem., 52, 4665, 1987. The choice of a particular reduction method is made by one skilled in the art, depending on the nature of the substituent groups attached to the cinnamic acid ester 138.3.

Alternatively, the cinnamic esters 138.3 are obtained by means of a palladium-catalyzed Heck

15 reaction between an appropriately substituted bromobenzene 138.5 and ethyl acrylate 138.4.

In this procedure, a substituted bromobenzene 138.5 is reacted with ethyl acrylate in the presence of a palladium (II) catalyst, as described in J. Med. Chem., 35, 1371, 1992, to afford the cinnamate ester 138.3. Equimolar amounts of the reactants 138.4 and 138.5 are dissolved in a polar aprotic solvent such as dimethylformamide or tetrahydrofuran, at a temperature of

20 about 60°C, in the presence or ca. 3 mol % of, for example, bis(triphenylphosphine)palladium (II) chloride and triethylamine, to afford the product 138.3.

Alternatively, the substituted phenylpropionic acid intermediates are obtained from the correspondingly substituted methylbenzenes 138.7. In this procedure, the methylbenzene 138.7 is subjected to free-radical bromination, for example by reaction with an equimolar

25 amount of N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative 138.8. The latter compound is then reacted with a salt of an ester of malonic acid, for example the sodium salt of diethyl malonate 138.9, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 489, to afford the displacement product 138.6, (X = COOEt). The latter compound is subjected to hydrolysis

30 and decarboxylation, for example by treatment with aqueous alkali or dilute aqueous acid, to afford the phenylpropionic acid 138.10.

Scheme 139 illustrates the preparation of phosphonate-containing phenylpropionic acids in which the phosphonate moiety is attached to the phenyl ring by means of an aromatic group. In this procedure, the carboxyl group of a bromo-substituted phenylpropionic acid 139.1 is protected. Methods for the protection of carboxylic acids are described, for example, in

5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 224. The product 139.2 is then subjected to halogen-methyl exchange, for example by reaction with an alkyllithium, to afford the product 139.3 in which M is Li. The latter compound is subjected to palladium (II) or palladium (0) catalyzed coupling, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

10 Compound 139.3 is first converted into the boronic acid 139.4, by reaction with a trialkyl borate, and the boronic acid product is coupled with a dialkyl bromophenylphosphonate 139.5 to yield the product 139.6. Deprotection then affords the intermediate phosphonate-substituted phenylpropionic acid 139.7.

For example, 4-bromophenylpropionic acid 139.8, prepared as described in U.S. 4,032,533, is
15 converted into the acid chloride, by treatment with thionyl chloride, oxalyl chloride and the like. The acid chloride is then reacted with 3-methyl-3-oxetanemethanol 139.9 (Aldrich), in the presence of a tertiary organic base such as pyridine, in a solvent such as dichloromethane, to afford the ester 139.10. This product is then rearranged by treatment with boron trifluoride etherate in dichloromethane, at about -15°C as described in Protective Groups in Organic

20 Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 268, to yield the orthoester 139.11, known as an OBO ester. The latter product is then reacted with one molar equivalent of n-butyllithium, in a solvent such as ether, at about -80°C, to afford the lithio derivative, which is reacted with a trialkyl borate, as described in J. Organomet. Chem., 1999, 581, 82, to yield the boronate 139.12. This material is coupled, in the presence of a catalytic

25 amount of tetrakis(triphenylphosphine)palladium(0), and an inorganic base such as sodium carbonate, with a dialkyl 4-bromophenylphosphonate 139.13, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 139.14. Deprotection, for example by treatment with aqueous pyridine p-toluenesulfonate, as described in Can. J. Chem., 61, 712, 1983, then affords the carboxylic acid 139.15.

30 Using the above procedures, but employing, in place of the 4-bromophenylpropionic acid 139.8, different bromophenylpropionic acids 139.1, and/or different dialkyl bromophenyl phosphonates 139.5, the corresponding products 139.7 are obtained.

Scheme 140 depicts the preparation of phenylpropionic acids in which a phosphonate ester is attached to the phenyl ring by means of a heteroatom. In this procedure, a suitably protected hydroxy, thio or amino-substituted phenyl propionic acid 140.1 is reacted with a derivative of

5 a hydroxymethyl dialkylphosphonate 140.2, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product 140.3.

Deprotection then affords the carboxylic acid 140.4.

For example, trichloroethyl 3-hydroxyphenylpropionic acid 140.5, prepared by reaction of 3-

10 hydroxyphenylpropionic acid (Fluka) with trichloroethanol and dicyclohexylcarbodiimide, as described in J. Am. Chem. Soc., 88, 852, 1966, is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 140.6, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product 140.7. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as

15 potassium carbonate, at about 50°C, to afford the product 140.7. Removal of the trichloroethyl ester group, for example by treatment with zinc in acetic acid at 0°C, as described in J. Am. Chem. Soc., 88, 852, 1966, then yields the carboxylic acid 140.8.

Using the above procedures, but employing, in place of the phenol 140.5, different phenols, thiols or amines 140.1, and/or different phosphonates 140.2, the corresponding products 140.4

20 are obtained.

Scheme 141 illustrates the preparation of phenylpropionic acids in which a phosphonate moiety is attached by means of a chain incorporating a heteroatom. In this procedure, a carboxyl protected halomethyl substituted phenylpropionic acid 141.1 is reacted with a dialkyl

25 hydroxy, thio or amino-substituted alkylphosphonate 141.2. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 141.2. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate

30 and the like is employed.

For example, 4-bromomethyl phenylpropionic acid, prepared as described in U.S. 4,032,533, is converted into the methoxymethyl ester 141.5, by reaction with methoxymethyl chloride and

triethylamine in dimethylformamide, as described in J. Chem. Soc, 2127, 1965. Equimolar amounts of the ester **141.5** and a dialkyl 2-aminoethyl phosphonate **141.6**, prepared as described in J. Org. Chem., 2000, 65, 676, are reacted in dimethylformamide at ca 80°C, in the presence of potassium carbonate, to afford the displacement product **141.7**. Deprotection, for example by treatment with trimethylsilyl bromide and a trace of methanol, as described in Aldrichimica Acta, 11, 23, 1978, then yields the carboxylic acid **141.8**.

Using the above procedures, but employing, in place of the amine **141.6**, different amines, alcohols or thiols **141.2** and/or different halomethyl-substituted phenylpropionic acids **141.1**, the corresponding products **141.4** are obtained.

Scheme **142** illustrates the preparation of phosphonate esters attached to the phenyl ring by means of an oxygen or sulfur link, by means of a Mitsunobu reaction. In this procedure, a protected hydroxy- or thio-substituted phenylpropionic acid **142.1** is reacted with a dialkyl hydroxyalkyl phosphonate **142.2**. The condensation reaction between **142.1** and **142.2** is effected in the presence of a triaryl phosphine and diethyl azodicarboxylate, as described in Org. React., 1992, 42, 335. The product **142.3** is then deprotected to afford the carboxylic acid **142.4**.

For example, 3-mercaptophenylpropionic acid (Apin Chemicals) is converted into the tert. butyl ester **142.5**, by treatment with carbonyl diimidazole, tert. butanol and

diazabicycloundecene, as described in Synthesis, 833, 1982. The ester is reacted with a dialkyl hydroxymethylphosphonate **142.6**, prepared as described in Synthesis, 4, 327, 1998, in the presence of triphenyl phosphine, triethylamine and diethyl azodicarboxylate, to afford the thioether **142.7**. The tert. butyl group is removed by treatment with formic acid at ambient temperature, as described in J. Org. Chem., 42, 3972, 1977, to yield the carboxylic acid **142.8**.

Using the above procedures, but employing, in place of the thiol **142.5**, different phenols or thiols **142.1** and/or different hydroxyalkyl phosphonates **142.2**, the corresponding products **142.4** are obtained.

Scheme **143** depicts the preparation of phenylpropionic acids linked to a phosphonate ester by means of an aromatic or heteroaromatic ring. The products **143.3** are obtained by means of an alkylation reaction in which a bromomethyl aryl or heteroaryl phosphonate **143.1** is reacted with a carboxyl-protected hydroxy, thio or amino-substituted phenylpropionic acid **140.1**. The

reaction is conducted in the presence of a base, the nature of which is determined by the substituent X in the reactant **140.1**. For example, if X is O, a strong base such as lithium hexamethyldisilylazide or sodium hydride is employed. If X is S or N, an organic or inorganic base, such as diisopropylethylamine or cesium carbonate is employed. The alkylated product

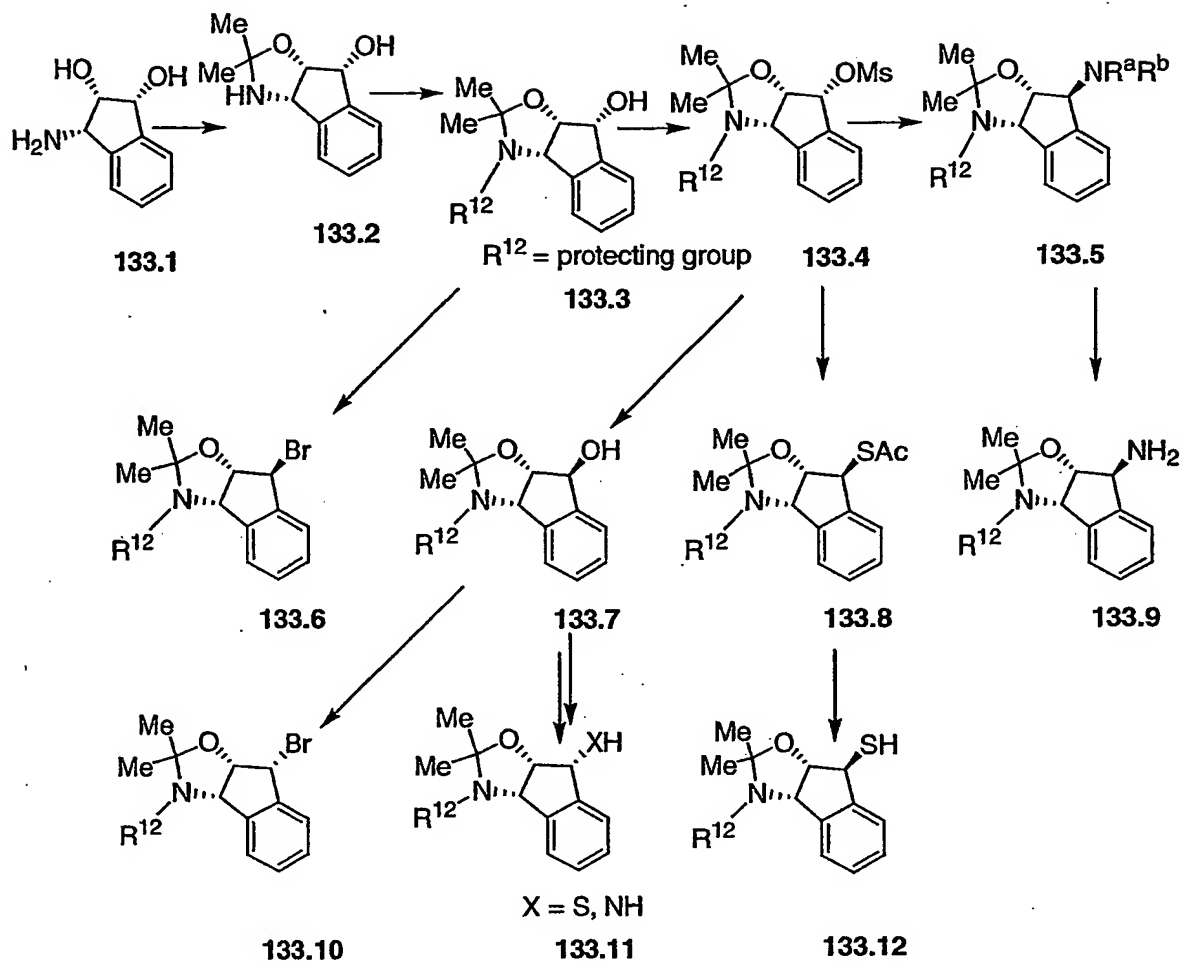
5 **143.2** is then deprotected to afford the carboxylic acid **143.3**.

For example, 3-(4-aminophenyl)propionic acid (Aldrich) is reacted with tert. butyl chlorodimethylsilane and imidazole in dimethylformamide, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 262, to afford the silyl ester **143.4**. This compound is reacted with an equimolar amount of a

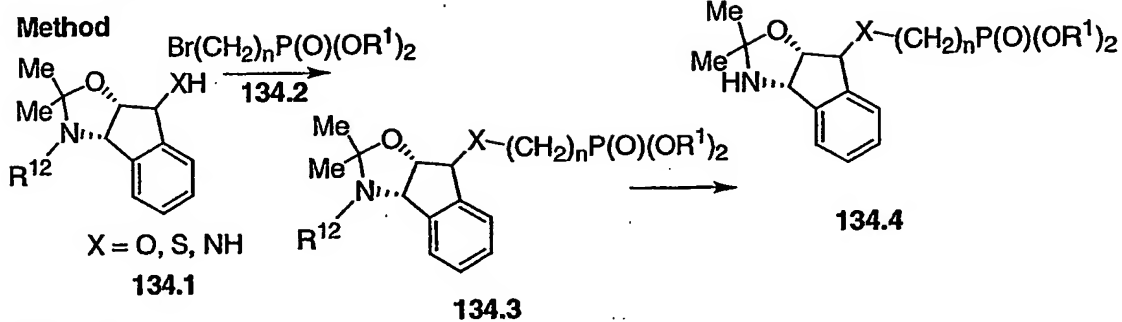
10 dialkyl 4-bromomethylbenzylphosphonate **143.5**, prepared as described in Tet. Lett., 1998, 54, 9341, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the product **143.6**. The silyl ester is removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to give the carboxylic acid **143.7**.

15 Using the above procedures, but employing, in place of the amino compound **143.4**, different phenols, mercaptans or amines **140.1**, and/or different halomethyl phosphonates **143.1**, the corresponding products **143.3** are obtained.

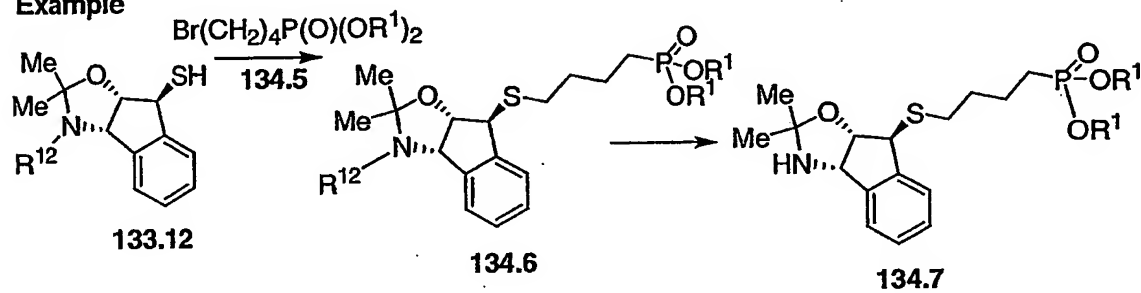
Scheme 133



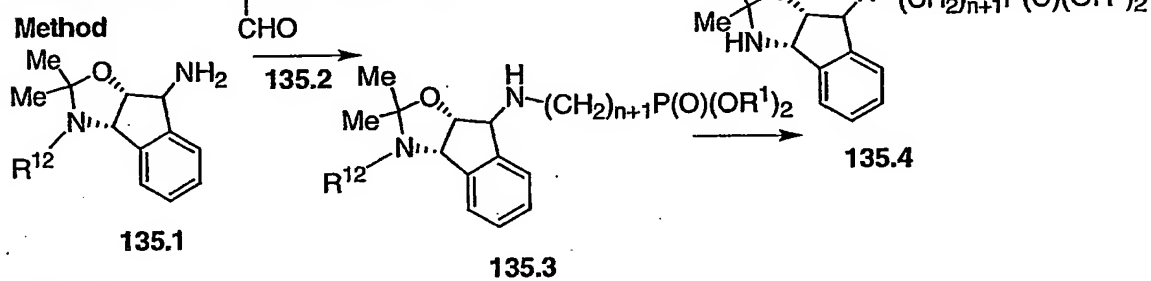
Scheme 134



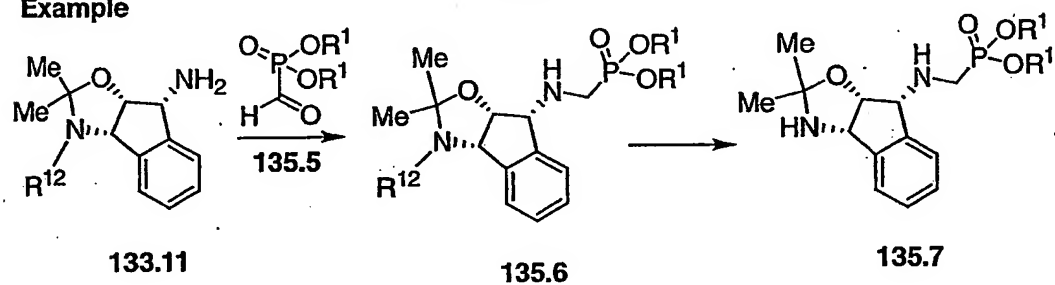
Example

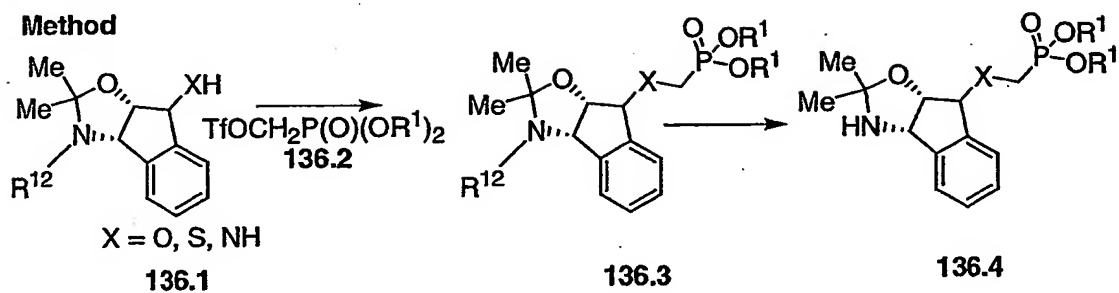
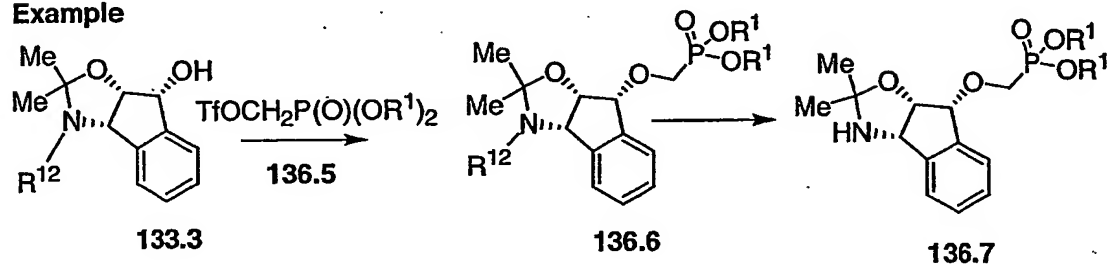
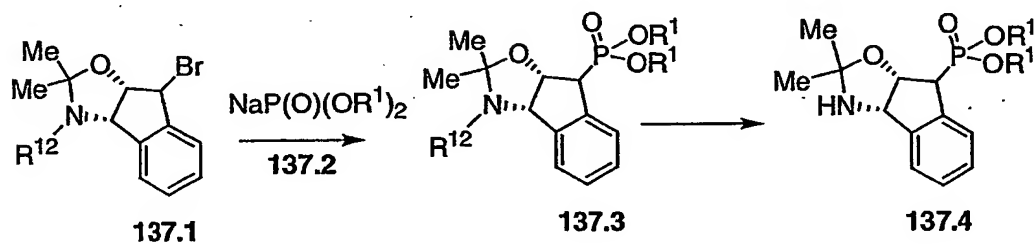
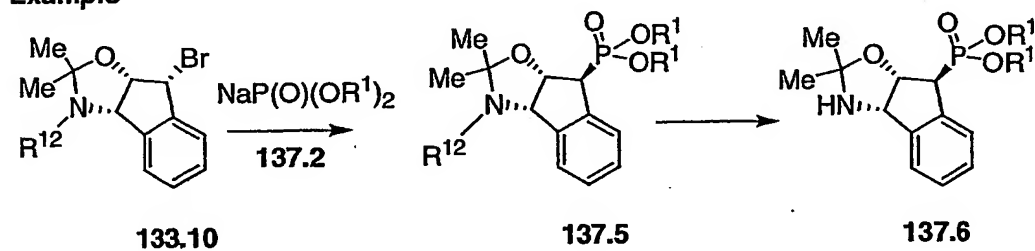


Scheme 135

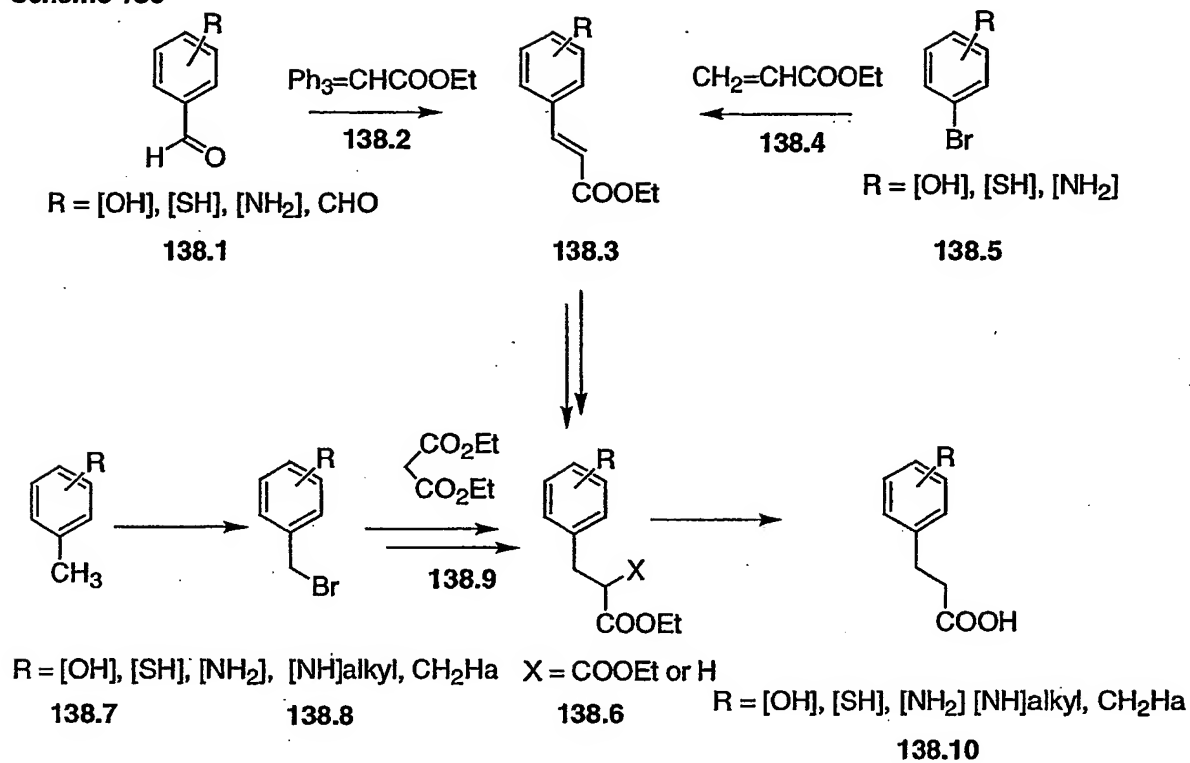


Example



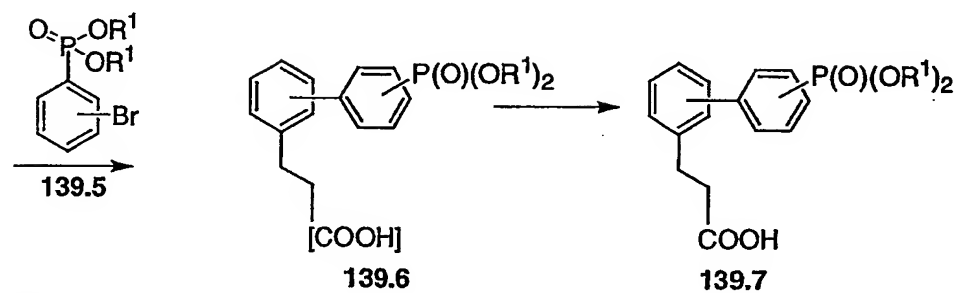
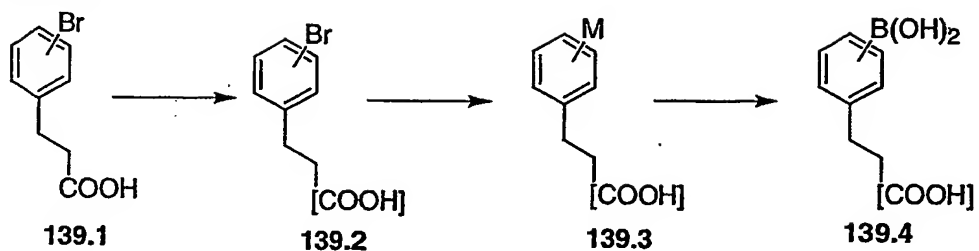
Scheme 136**Method****Example****Scheme 137****Method****Example**

Scheme 138

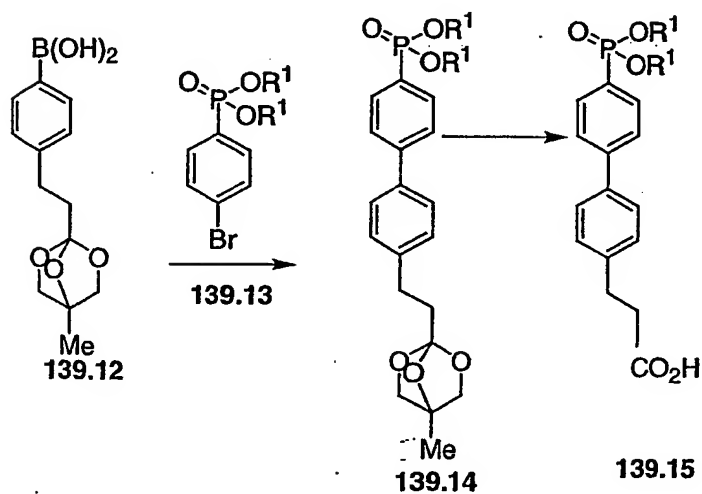
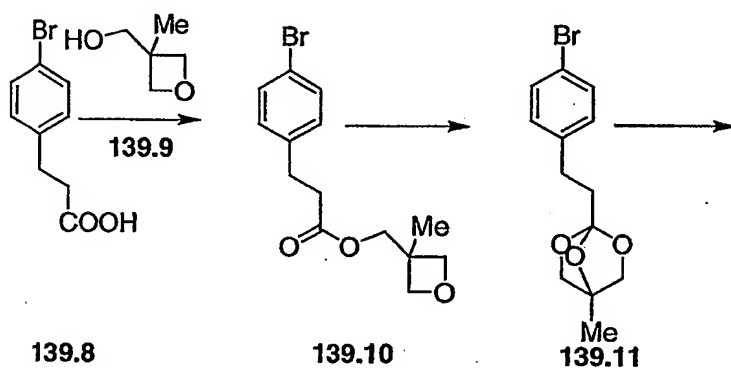


Scheme 139

Method

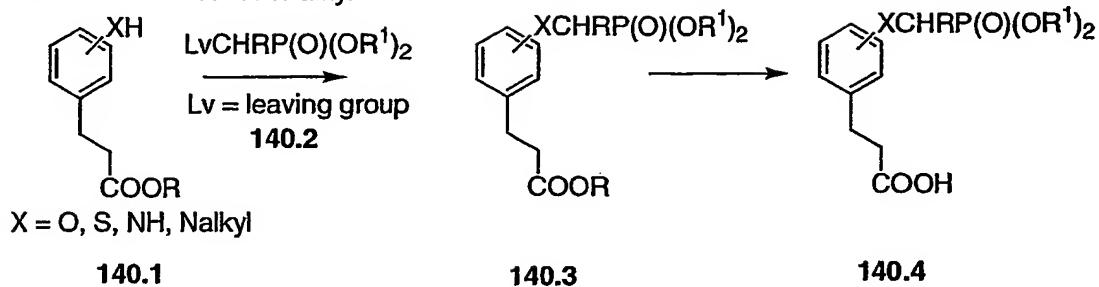
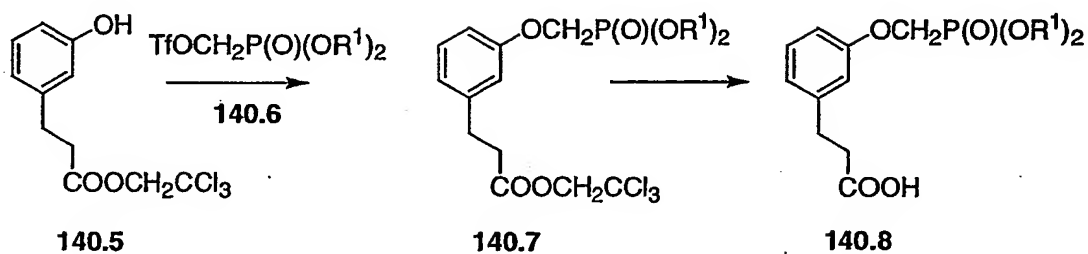
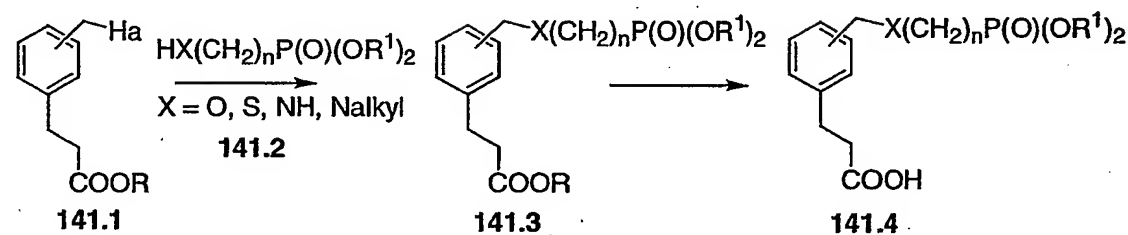
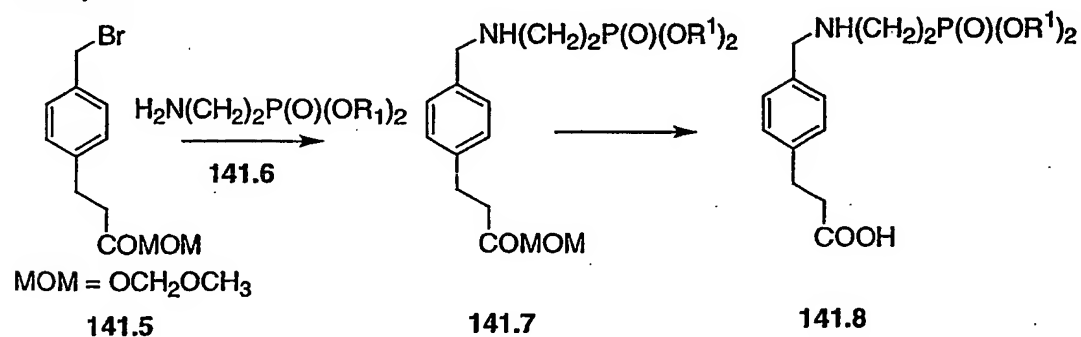


Example



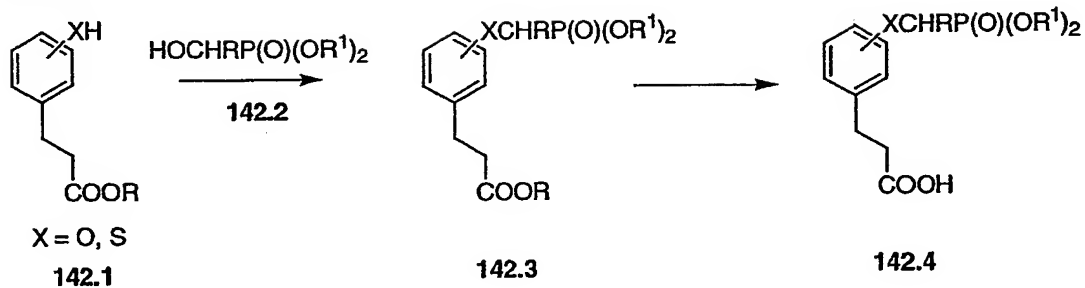
Scheme 140**Method**

R = H or alkyl

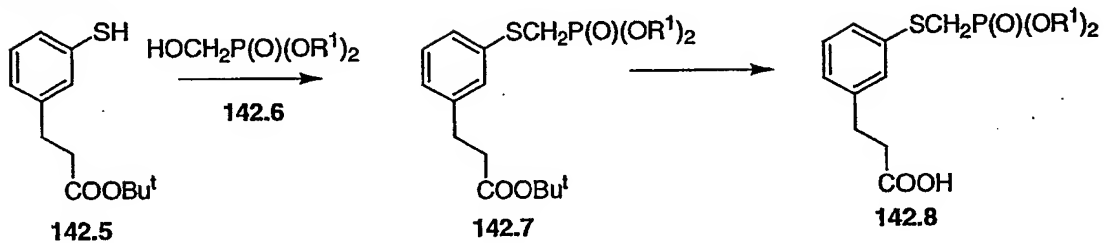
**Example****Scheme 141****Method****Example**

Scheme 142

Method

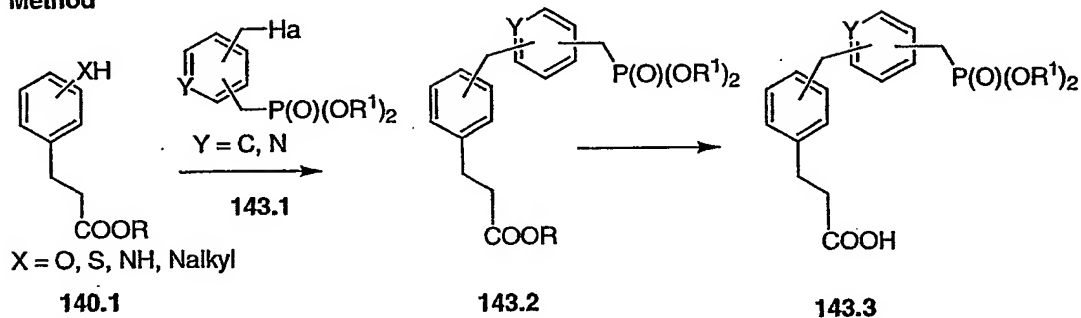


Example

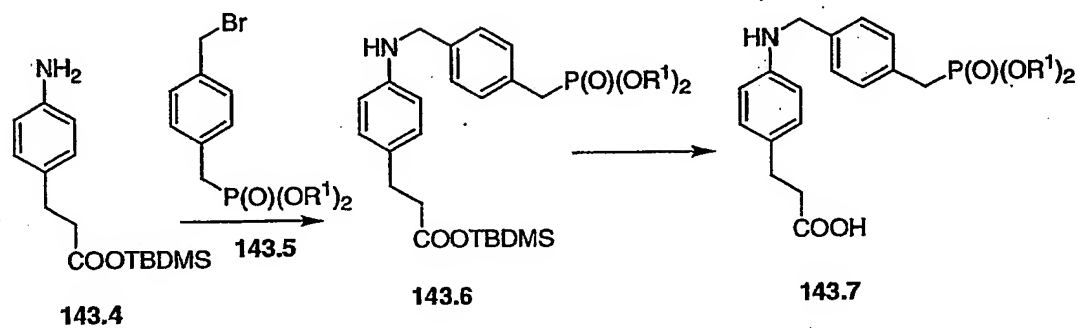


Scheme 143

Method



Example



Preparation of the phosphonate-containing thiophenol derivatives 7.1.

Schemes 144 - 153 describe the preparation of phosphonate-containing thiophenol derivatives 7.1 which are employed in the preparation of the phosphonate ester intermediates 2, 14 and 19 in which X is sulfur, and of the intermediate 15 in which X' is sulfur.

Scheme 144 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 144.1 is protected to afford the product 144.2. The protection and deprotection of thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 144.3, to afford the phosphonate ester 144.4. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The thiol protecting group is then removed, as described above, to afford the thiol 144.5.

For example, 3-bromothiophenol 144.6 is converted into the 9-fluorenylmethyl (Fm) derivative 144.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 144.3 to afford the phosphonate ester 144.8. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The compound 144.7 is reacted, in toluene solution at reflux, with a dialkyl phosphite 144.3, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 144.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 144.9.

Using the above procedures, but employing, in place of 3-bromothiophenol 144.6, different thiophenols 144.1, and/or different dialkyl phosphites 144.3, the corresponding products 144.5 are obtained.

5 Scheme 145 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 145.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 145.3. The latter compound is reacted with a halodialkyl phosphite 145.4 to afford the product 145.5; deprotection then affords the
10 thiophenol 145.6

For example, 4-bromothiophenol 145.7 is converted into the S-triphenylmethyl (trityl) derivative 145.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 287. The product is converted into the lithium derivative 145.9 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio
15 compound is reacted with a dialkyl chlorophosphite 145.10 to afford the phosphonate 145.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 145.12.

Using the above procedures, but employing, in place of the bromo compound 145.7, different halo compounds 145.1, and/or different halo dialkyl phosphites 145.4, there are obtained the
20 corresponding thiols 145.6.

Scheme 146 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 146.1 is subjected to free-radical bromination to
25 afford a bromomethyl product 146.2. This compound is reacted with a sodium dialkyl phosphite 146.3 or a trialkyl phosphite, to give the displacement or rearrangement product 146.4, which upon deprotection affords the thiophenol 146.5.

For example, 2-methylthiophenol 146.5 is protected by conversion to the benzoyl derivative 146.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 146.8. This material is reacted with a sodium dialkyl
30 phosphite 146.3, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 146.9.

Alternatively, the bromomethyl compound **146.8** is converted into the phosphonate **146.9** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **146.8** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. $100^\circ C$ to produce the phosphonate **146.9**. Deprotection of the phosphonate **146.9**, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol **146.10**.

Using the above procedures, but employing, in place of the bromomethyl compound **146.8**, different bromomethyl compounds **146.2**, there are obtained the corresponding thiols **146.5**.

Scheme **147** illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **147.1** is reacted with a dialkyl hydroxyalkylphosphonate **147.2** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product **147.3**. Deprotection then yields the O- or S-linked products **147.4**.

For example, 3-hydroxythiophenol, **147.5**, is converted into the monotrityl ether **147.6**, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate **147.7** in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound **147.8**.

Removal of the trityl protecting group, as described above, then affords the thiophenol **147.9**. Using the above procedures, but employing, in place of the phenol **147.5**, different phenols or thiophenols **147.1**, there are obtained the corresponding thiols **147.4**.

Scheme **148** illustrates the preparation of thiophenols **148.4** bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol **148.1** is reacted with an activated ester, for example the trifluoromethanesulfonate **148.2**, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product **148.3**. Deprotection then affords the thiol **148.4**.

For example, 4-methylaminothiophenol **148.5** is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 298, to afford the S-acetyl product **148.6**. This material is then reacted with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate 148.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 148.8. Preferably, equimolar amounts of the phosphonate 148.7 and the amine 148.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient
5 temperatures, to afford the phosphonate product 148.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 148.9.

Using the above procedures, but employing, in place of the thioamine 148.5, different phenols, thiophenols or amines 148.1, and/or different phosphonates 148.2, there are obtained the
10 corresponding products 148.4.

Scheme 149 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 149.2. In this procedure, a suitably protected
15 hydroxy, thio or amino substituted thiophenol 149.1 is reacted with a dialkyl bromoalkyl phosphonate 149.2 to afford the product 149.3. Deprotection then affords the free thiophenol 149.4.

For example, 3-hydroxythiophenol 149.5 is converted into the S-trityl compound 149.6, as described above. This compound is then reacted with a dialkyl 4-bromobutyl phosphonate
20 149.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°C to yield the ether product 149.8. Deprotection, as described above, then affords the thiol 149.9.

25 Using the above procedures, but employing, in place of the phenol 149.5, different phenols, thiophenols or amines 149.1, and/or different phosphonates 149.2, there are obtained the corresponding products 149.4.

Scheme 150 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by
30 means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 150.2 is coupled with an aromatic bromo compound 150.1. The coupling of aryl halides with olefins

- by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
- 5 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **150.3**. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate **150.4**, or the saturated analog **150.6**.
- 10 For example, 3-bromothiophenol is converted into the S-Fm derivative **150.7**, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate **150.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
- 15 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **150.9**. Deprotection, as described above, then affords the thiol **150.10**. Optionally, the initially formed unsaturated phosphonate **150.9** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme **138**, to yield the saturated product **150.11**, which upon deprotection affords the thiol **150.12**.
- 20 Using the above procedures, but employing, in place of the bromo compound **150.7**, different bromo compounds **150.1**, and/or different phosphonates **150.2**, there are obtained the corresponding products **150.4** and **150.6**

- Scheme **151** illustrates the preparation of an aryl-linked phosphonate ester **151.4** by means of
- 25 a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **151.1** is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in *J. Org. Chem.*, 49, 5237, 1984. A coupling reaction then affords the
- 30 diaryl product **151.3** which is deprotected to yield the thiol **151.4**. For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in *Protective Groups in Organic*

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **151.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **151.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **151.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **151.8**. Using the above procedures, but employing, in place of the boronate **151.5**, different boronates **151.1**, and/or different phosphonates **151.2**, there are obtained the corresponding products **151.4**.

Scheme 152 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **152.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **152.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **152.3** is then deprotected to afford the thiol **152.4**.

For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **152.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **152.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **152.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C. The thioether product **152.7** thus obtained is deprotected, as described above, to afford the thiol **152.8**.

Using the above procedures, but employing, in place of the thiophenol **152.5**, different phenols, thiophenols or amines **152.1**, and/or different phosphonates **152.2**, there are obtained the corresponding products **152.4**.

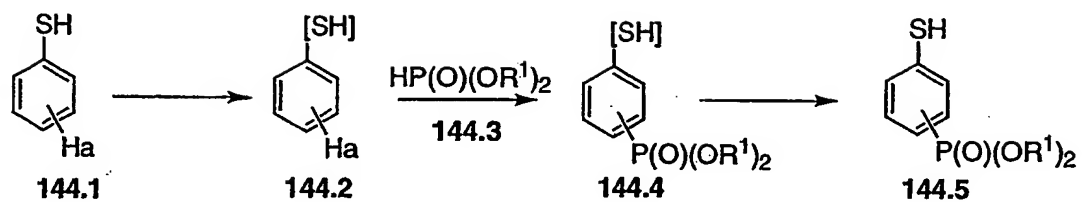
Scheme 153 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol 153.1, for example an indoline (in which X-Y is $(\text{CH}_2)_2$), an indole (X-Y is $\text{CH}=\text{CH}$) or a tetrahydroquinoline (X-Y is $(\text{CH}_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 153.2, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 153.3. Deprotection, as described above, then affords the thiol 153.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines are also obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, 153.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 153.6, as described above, and the ester is then reacted with the trifluoromethanesulfonate 153.7, using the conditions described above for the preparation of the phosphonate 148.8, (Scheme 148), to yield the phosphonate 153.8. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol 153.9.

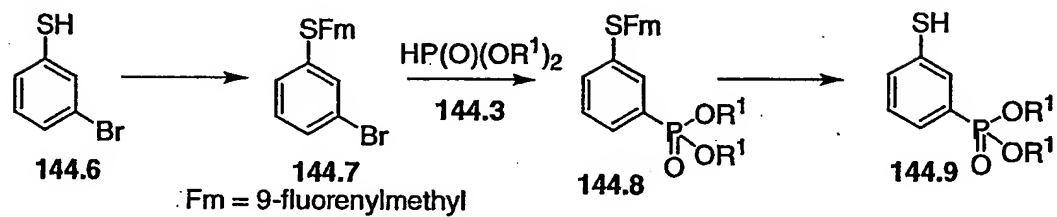
Using the above procedures, but employing, in place of the thiol 153.5, different thiols 153.1, and/or different triflates 153.2, there are obtained the corresponding products 153.4.

Scheme 144

Method

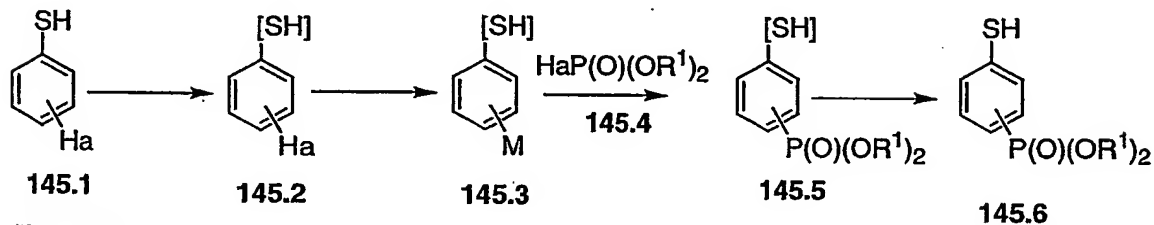


Example

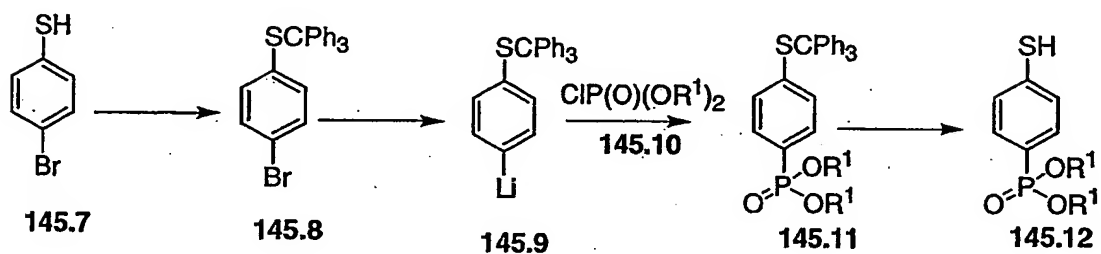


Scheme 145

Method

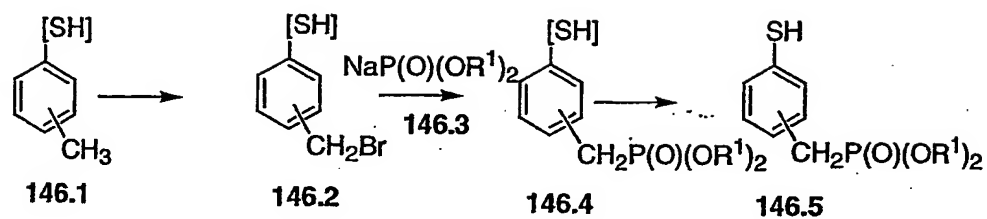


Example

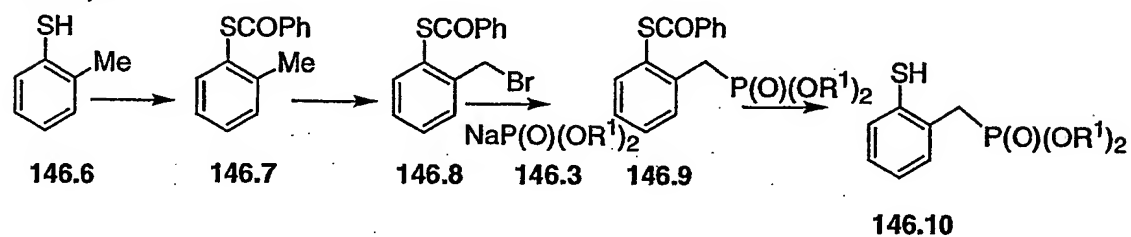


Scheme 146

Method

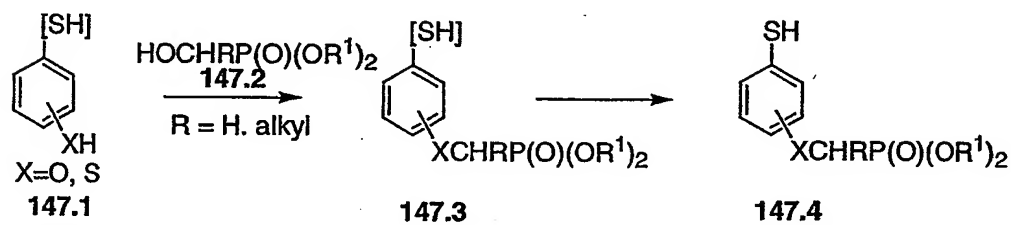


Example

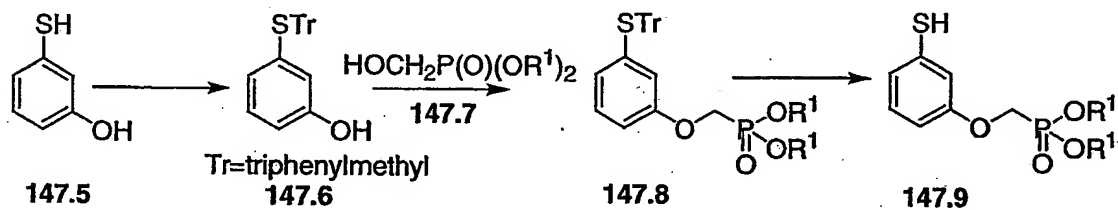


Scheme 147

Method

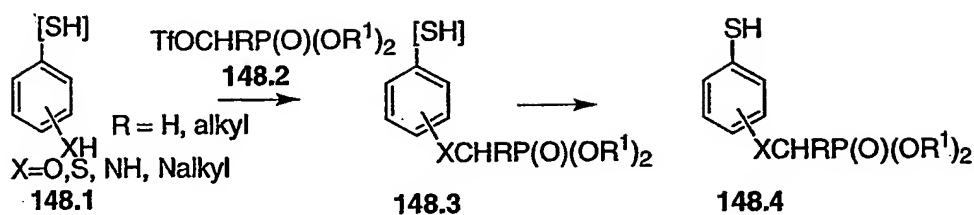


Example

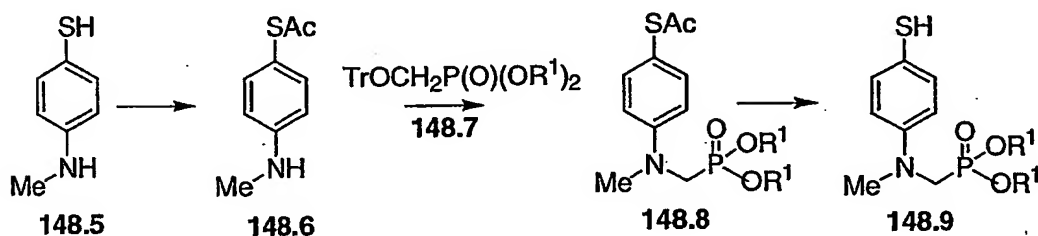


Scheme 148

Method

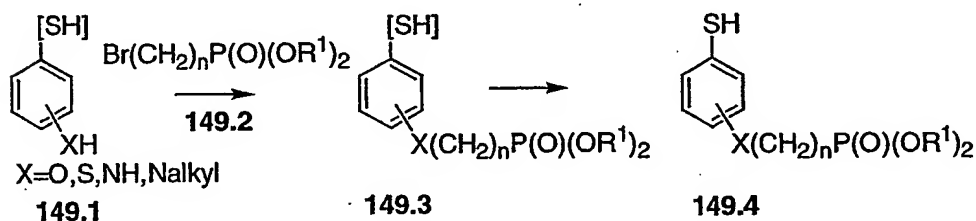


Example

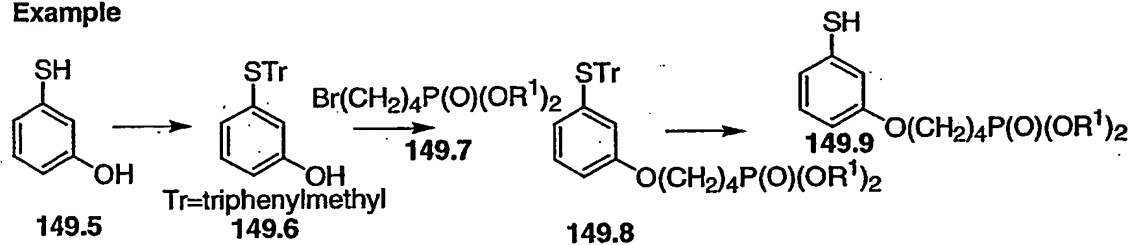


Scheme 149

Method

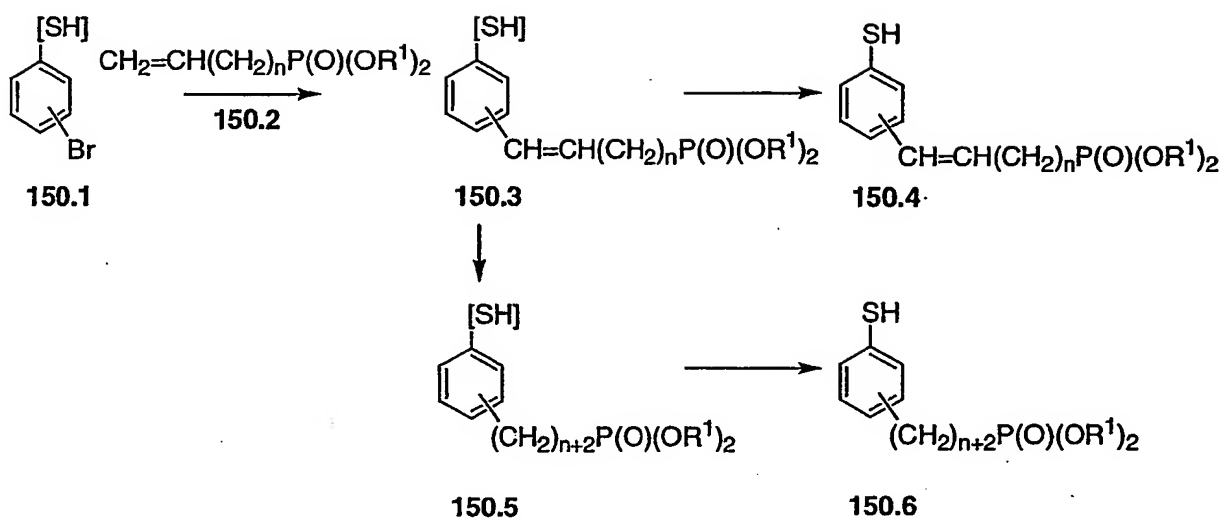


Example

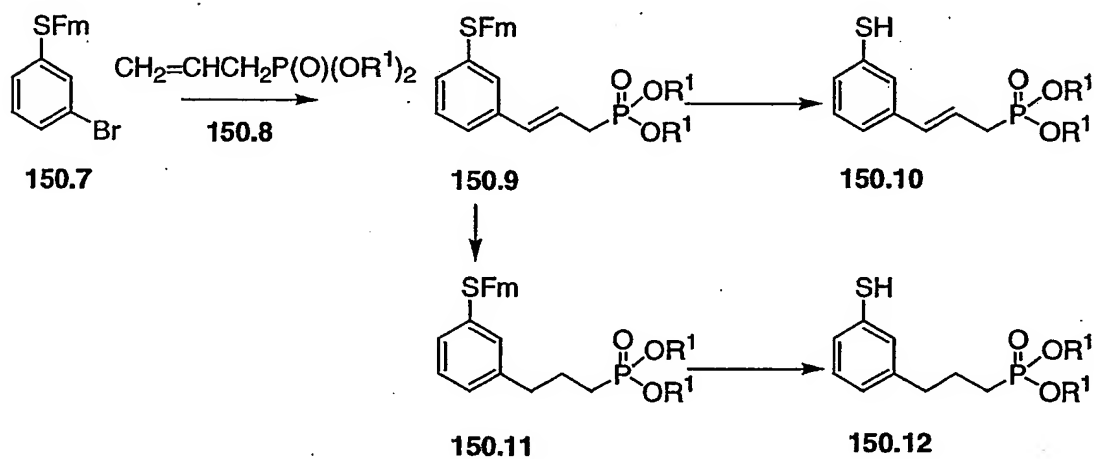


Scheme 150

Method

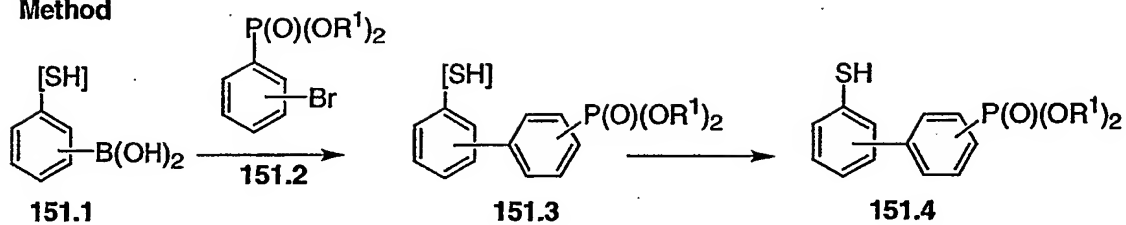


Example

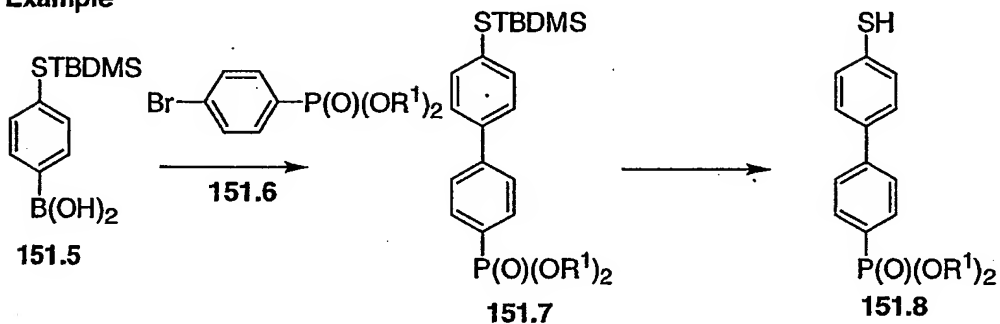


Scheme 151

Method

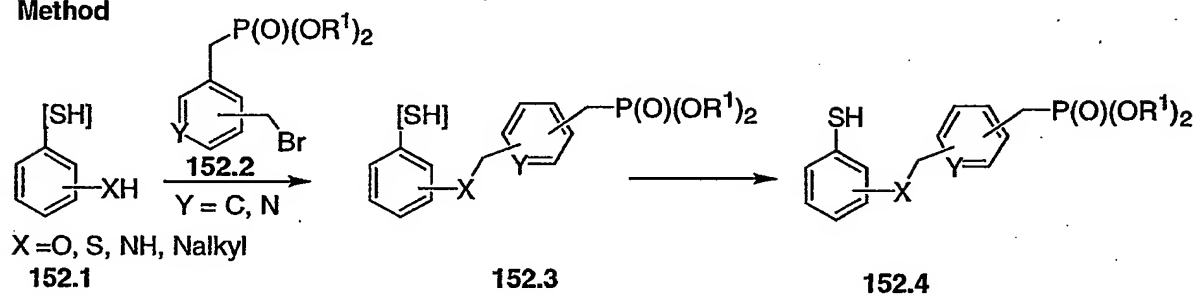


Example

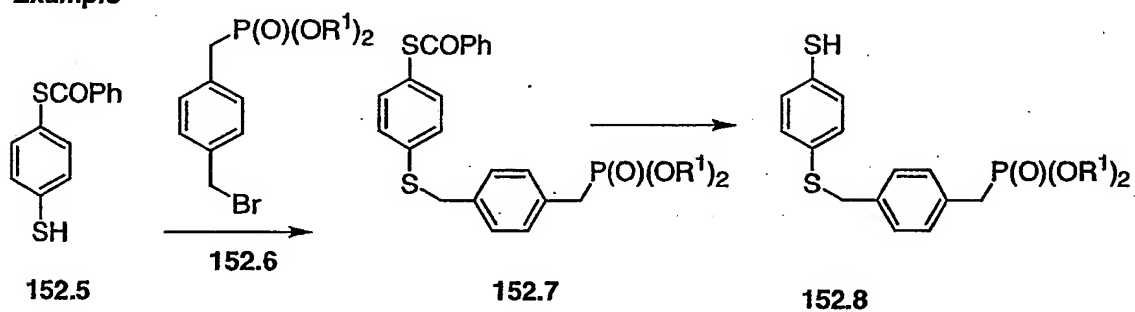


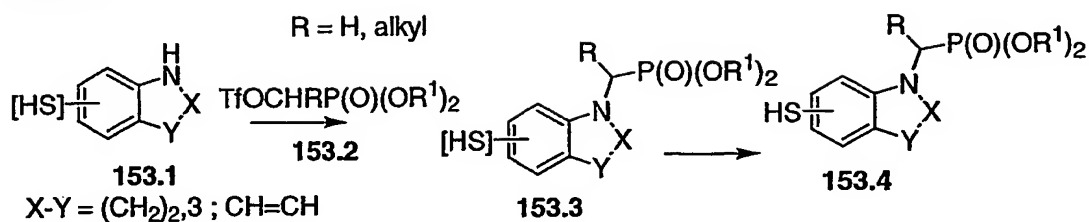
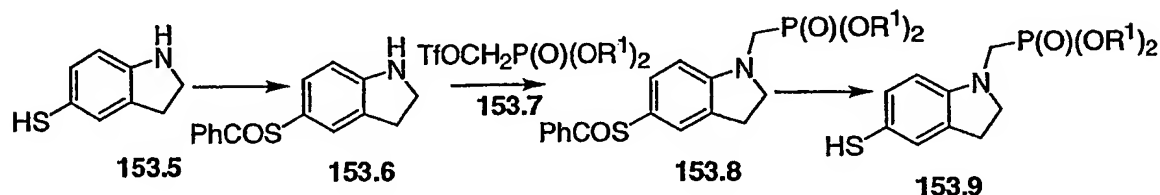
Scheme 152

Method



Example



Scheme 153**Method****Example**

Preparation of tert-butylamine derivatives 9.3 and 25.4 incorporating phosphonate groups.

5

Schemes 154 – 158 illustrate the preparation of the tert. butylamine derivatives 9.3 and 25.4 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br, which are employed in the preparation of the intermediate phosphonate esters 3, 7, 11 and 20.

10

Scheme 154 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl bromide 154.1 is reacted with a trialkyl phosphite 154.2, under the conditions of the Arbuzov reaction, as described in Scheme 137, to afford the phosphonate 154.3, which is then deprotected to give the amine 154.4.

15

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide 154.6, is heated with a trialkyl phosphite at ca 150°C to afford the product 154.7. Deprotection then affords the free amine 154.8. The removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion is effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group is removed by treatment of the substrate with triethylsilane,

20

triethylamine and a catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group is also removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 5 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979.

Using the above procedures, but employing different trialkyl phosphites, there are obtained the corresponding amines 154.4.

Scheme 155 illustrates the preparation of phosphonate esters attached to the tert butylamine 10 by means of a heteroatom and a carbon chain. A protected alcohol or thiol 155.1 is reacted with a dialkyl bromoalkylphosphonate 155.2, to afford the displacement product 155.3. Deprotection, if needed, then yields the amine 155.4.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol 155.5 is reacted with a dialkyl 4-bromobutyl phosphonate 155.6, prepared as described in Synthesis, 1994, 9, 909, in 15 dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate 155.7. Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine 155.8.

Using the above procedures, but employing different alcohols or thiols 155.1, and/or different bromoalkylphosphonates 155.2, there are obtained the corresponding ether and thioether 20 products 155.4.

Scheme 156 describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain is unsaturated or saturated.

In the procedure, a terminal acetylenic derivative of tert-butylamine 156.1 is reacted, under 25 basic conditions, with a dialkyl chlorophosphite 156.2, to afford the acetylenic phosphonate 156.3. The coupled product 156.3 is deprotected to afford the amine 156.4. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products 156.5 and 156.6 respectively.

For example, 2-amino-2-methylprop-1-yne 156.7, the preparation of which is described in WO 30 9320804, is converted into the N-phthalimido derivative 156.8, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide

in tetrahydrofuran at -78°C . The resultant anion is then reacted with a dialkyl chlorophosphite **156.2** to afford the phosphonate **156.9**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **156.10**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **156.11**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **156.12**. Using the above procedures, but employing different acetylenic amines **156.1**, and/or different dialkyl halophosphites, there are obtained the corresponding products **156.4**, **156.5** and **156.6**.

Scheme **157** illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

In this method, an aminopropyl-substituted cyclic amine **157.1** is reacted with a limited amount of a bromoalkyl phosphonate **157.2**, using, for example, the conditions described above (Scheme **149**) to afford the displacement product **157.3**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-bromobutyl phosphonate **157.5**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **157.6**.

Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine **157.4**, different cyclic amines **157.1**, and/or different bromoalkylphosphonates **157.2**, there are obtained the corresponding products **157.3**.

Scheme **158** illustrates the preparation of the amides **9.3** which are employed in the preparation of the phosphonate esters **3**. In this procedure, the carboxylic acids **158.1**, the structures of which are illustrated in Chart **10**, compounds **C1** - **C16**, are converted into the BOC-protected derivatives **155.8**. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine is reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON), and the like. The carboxylic acid

158.2 is then coupled, as described in Scheme 1, with the tert. butylamine derivatives 25.4, or precursors thereto, the preparation of which is described in Schemes 154 - 157, to afford the amide 158.3. The BOC group is then removed to yield the amine 9.3. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of pyridine intermediates 13.1 incorporating phosphonate substituents.

10

Schemes 159 - 163, described the preparation of chloromethyl or formyl pyridine derivatives incorporating phosphonate moieties. Scheme 164 illustrates the conversion of the above compounds into the piperazine derivatives 13.1 which are employed in the preparation of the phosphonate esters 4.

15

Scheme 159 illustrates the preparation of chloromethyl-substituted pyridines in which a phosphonate moiety is directly attached to the pyridine ring.

In this procedure, a halo-substituted methylpyridine 159.1 is reacted with a dialkyl phosphite 159.2, to afford the phosphonate product 159.3. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in J. Med. Chem., 35, 1371, 1992. The product 159.3 is then converted into the chloromethyl derivative 159.4 by means of a chlorination reaction. The chlorination of benzylic methyl groups is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. A variety of free-radical chlorinating agents are employed.

For example, 3-bromo-5-methylpyridine, 159.5 (ChemPacific) is reacted with an equimolar amount of a dialkyl sodium phosphite, 13.2 in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate 159.6. The latter compound is then chlorinated, for example by the use of one molar equivalent of phenyliodonium dichloride, as described in J. Org. Chem., 29, 3692, 1964, to prepare the chloromethyl compound 159.7.

Using the above procedures, but employing, in place of the bromomethyl pyridine 159.5, different halomethyl pyridines 159.1, and/or different dialkyl phosphites 159.2 the corresponding products 159.4 are obtained.

Scheme 160 depicts the preparation of chloromethyl pyridines incorporating a phosphonate group attached to the pyridine ring by means of a carbon link. In this procedure, a bis(chloromethyl)pyridine 160.1 is reacted with a sodium dialkyl phosphite 146.3, employing, for example, procedures described in J. Med. Chem., 35, 1371, 1992, to afford the displacement product 160.2.

For example, 3,5-bis(chloromethyl)pyridine 160.3, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, is reacted with one molar equivalent of a dialkyl sodium phosphite 146.3 in tetrahydrofuran, at ambient temperature, to afford the product 160.4.

Using the above procedures, but employing, in place of the bis(chloromethyl) compound 160.3, different bis(chloromethyl) pyridines 160.1, and/or different dialkyl sodium phosphites 146.3 the corresponding products 160.2 are obtained.

Scheme 161 illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine nucleus by means of a saturated or unsaturated carbon chain. In this procedure, a suitably protected halo-substituted pyridine carboxaldehyde 161.1 is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme 150, with a dialkyl alkenyl phosphonate 161.2. Methods for the protection of aldehydes are described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 175. The protected aldehyde 161.1 is reacted with an olefinic phosphonate 161.2, in the presence of a palladium (0) catalyst, to afford the coupled product 161.3. Deprotection of the aldehyde group then affords the product 161.6. Alternatively, the unsaturated compound 161.3 is reduced to afford the saturated analog 161.5, which upon deprotection yields the saturated analog 161.7. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, 5-bromopyridine-3-carboxaldehyde 161.8 (ChemPacific) is converted into the dimethyl acetal, by reaction with methanolic ammonium chloride, as described in J. Org. Chem., 26, 1156, 1961. The acetal 161.9 is then reacted with a dialkyl butenyl phosphonate 161.10, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in J. Med. Chem., 1992, 35, 1371, to afford the coupled product 161.11. Deprotection, for example by treatment with formic acid in pentane, as described in Synthesis, 651, 1983, yields the free aldehyde 161.13.

The product is reduced, for example by reaction with diimide, as described in J. Org. Chem., 30, 3965, 1965, to afford the saturated product **161.12**.

Using the above procedures, but employing, in place of the aldehyde **161.8**, different aldehydes **161.1**, and/or different phosphonates **161.2**, the corresponding products **161.6** and **161.7** are obtained.

Scheme **162** illustrates the preparation of pyridine aldehydes incorporating a phosphonate group linked to the pyridine by a heteroatom and a carbon chain. In this procedure, a 2- or 4-halo-substituted pyridine aldehyde **162.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **162.2**. The preparation of alkoxy- or thio-alkoxy-pyridines by the reaction of alkoxy- or thio-alkoxy-pyridines with alcohols or thiols is described, for example, in J. Am. Chem. Soc., 82, 4414, 1960. The preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in Chemistry of Heterocyclic Compounds, Pyridine and its derivatives, E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **162.3**.

For example, a tetrahydrofuran solution of 2-bromo-pyridine-5-aldehyde **162.4**, prepared as described in Tet. Lett., 2001, 42, 4841, is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **162.5**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **162.6**.

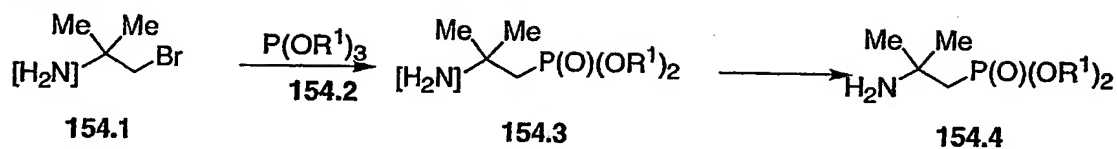
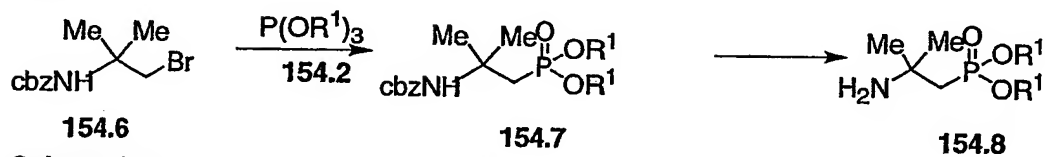
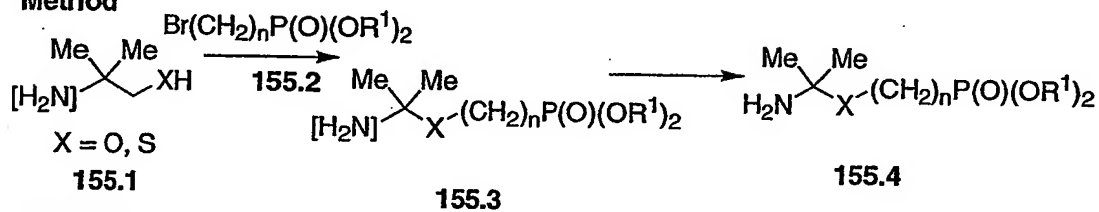
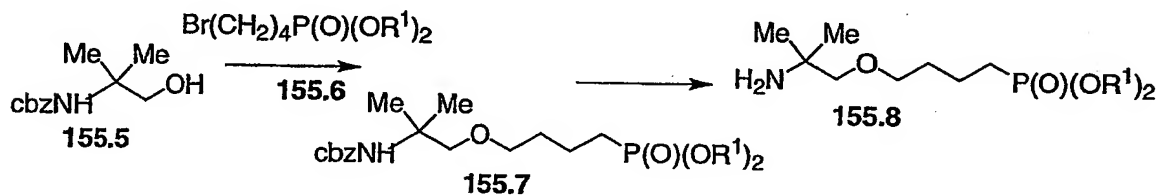
Using the above procedures, but employing, in place of the haloaldehyde **162.4**, different haloaldehydes **162.1**, and/or different hydroxy or thio-alkyl phosphonates **162.2**, the corresponding products **162.3** are obtained.

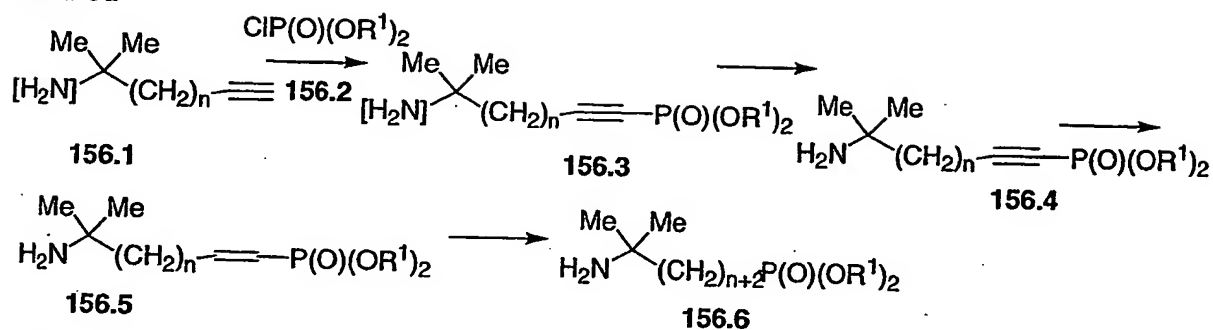
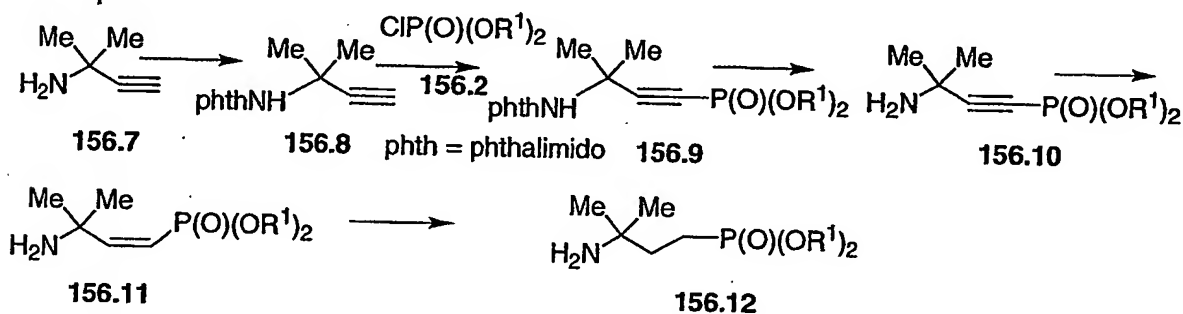
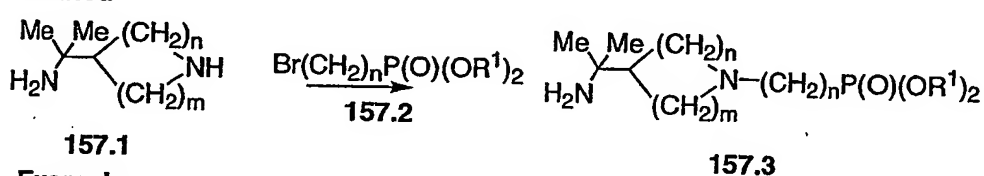
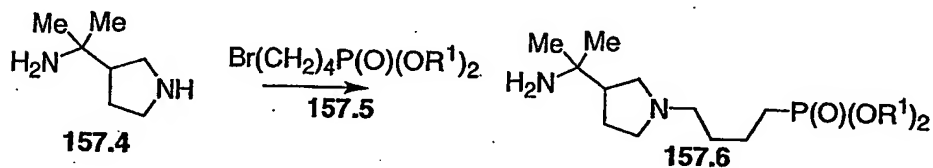
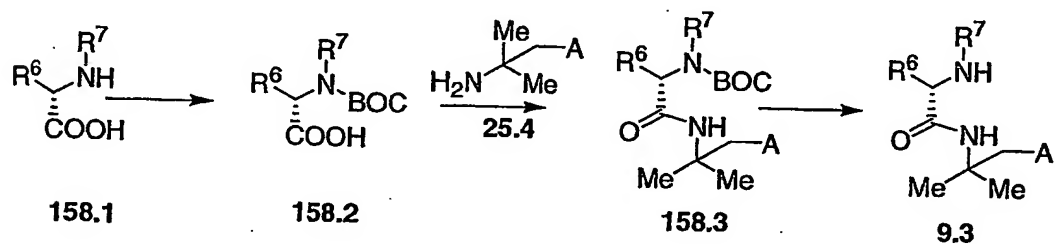
Scheme **163** depicts the preparation of pyridine aldehydes **163.3** in which the phosphonate group is attached to the pyridine nucleus by means of a chain incorporating a nitrogen atom. In this procedure, a pyridine dicarboxaldehyde **163.1** is reacted with a dialkyl aminoalkyl phosphonate **163.2**, in the presence of a reducing agent, so as to effect a reductive amination reaction, yielding the product **163.3**. The preparation of amines by means of reductive amination of aldehydes is described, for example, in Advanced Organic Chemistry, F. A.

Carey, R. J. Sundberg, Plenum, 2001, part B, p. 269. The reactants are combined in an inert solvent such as an alcohol or ether, and treated with a reducing agent such as, for example, sodium cyanoborohydride or sodium triacetoxy borohydride, so as to yield the amine product **163.3**.

- 5 For example, equimolar amounts of pyridine 3,5-dicarboxaldehyde **163.4**, prepared as described in Tet. Lett., 1994, 35, 6191, and a dialkyl 2-aminoethyl phosphonate **163.5** prepared as described in J. Org. Chem., 2000, 65, 676, are reacted with sodium cyanoborohydride in isopropanol containing acetic acid, at ambient temperature, so as to produce the amine product **163.6**
- 10 Using the above procedures, but employing, in place of the dicarboxaldehyde **163.4**, different dicarboxaldehydes **163.1**, and/or different aminoalkyl phosphonates **163.2**, the corresponding products **163.3** are obtained.

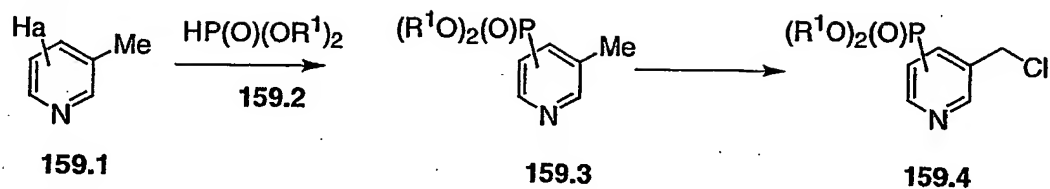
- Scheme **164** illustrates the incorporation of the formyl or chloromethyl pyridines, the syntheses of which are described above, into the piperazine reagent **13.1**. Compounds **164.2** in which Z is chloromethyl are reacted with the mono-protected piperazine derivatives **164.1**, the preparation of which are described in WO 9711698, to afford the alkylated product **164.3**. The preparation of amines by means of alkylation reactions is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 397. Equimolar amounts of the reactants **164.1** and the halomethyl pyridine compound **164.2**, are combined in a organic solvent such as an alcohol or dimethylformamide, in the presence of a base such as triethylamine or potassium carbonate, to give the alkylated products **164.3**. The alkylation of a piperazine derivative by a 3-chloromethylpyridine is described in WO9628439. Alternatively, the amine **164.1** is reacted with the aldehyde **164.2** to afford the product **164.3** in a reductive alkylation reaction. The preparation of amines by means of reductive amination procedures is described in Scheme **163**. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reductive alkylation reaction between 3-pyridinecarboxaldehyde and a substituted piperazine is described in WO9628439. Deprotection of the product **164.3** then yields the free amine **13.1**.

Scheme 154**Method****Example****Scheme 155****Method****Example**

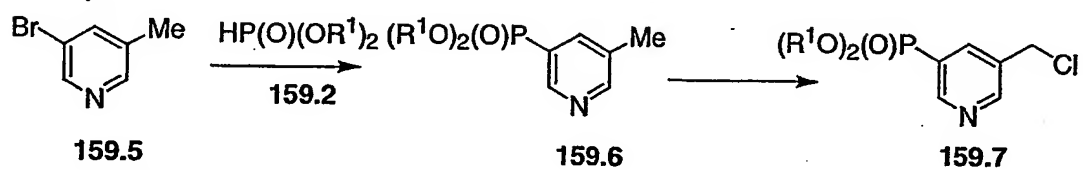
Scheme 156**Method****Example****Scheme 157****Method****Example****Scheme 158**

Scheme 159

Method

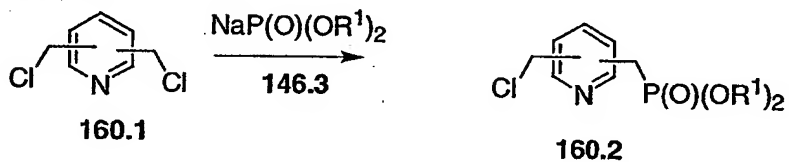


Example

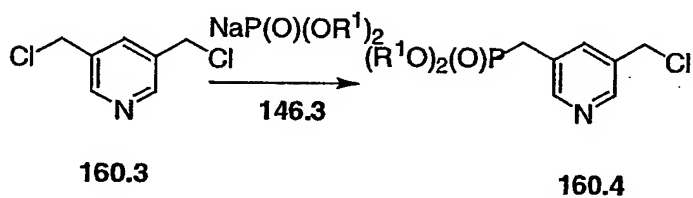


Scheme 160

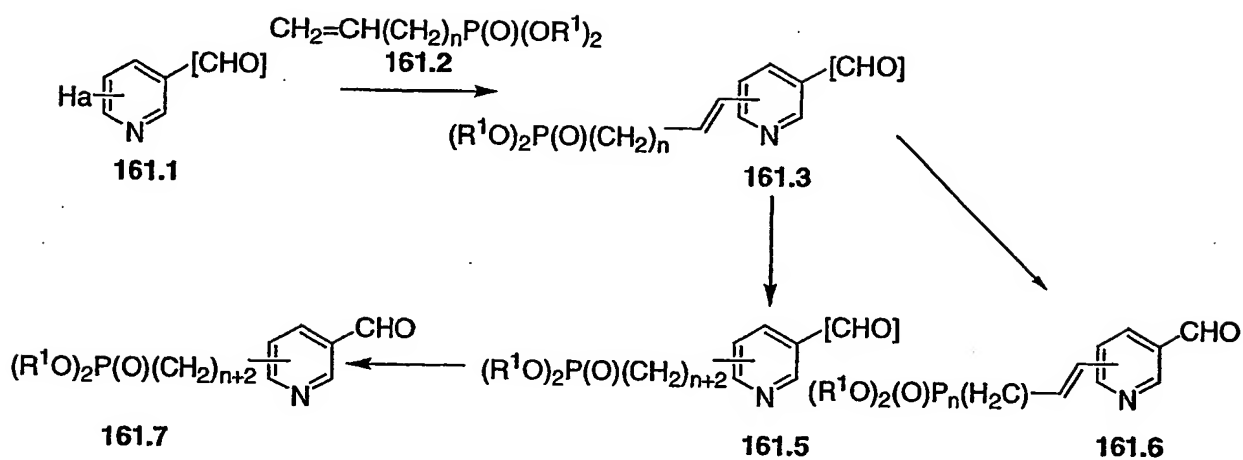
Method



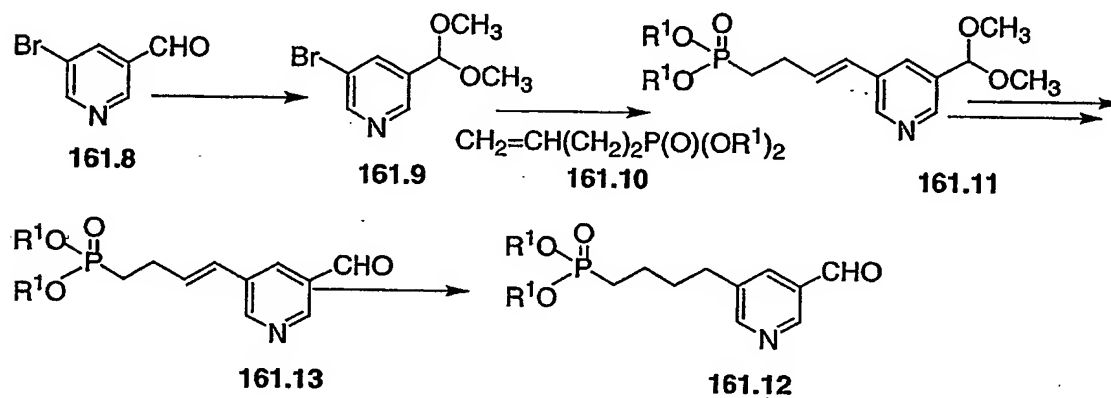
Example

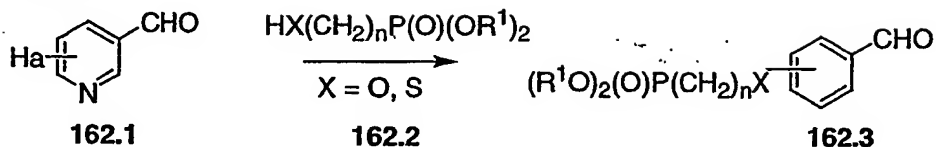
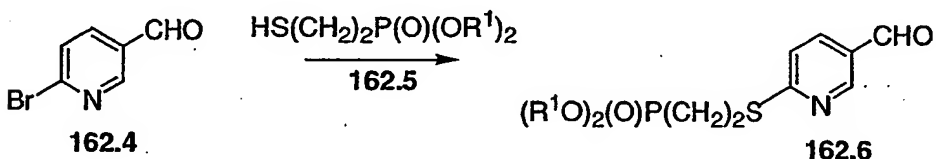
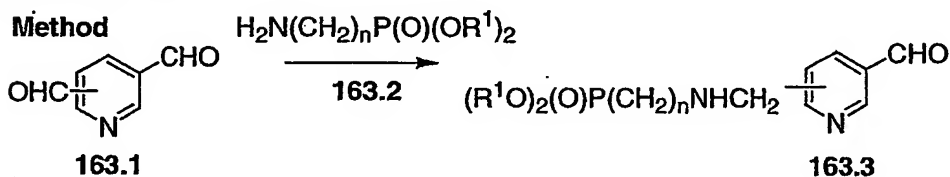
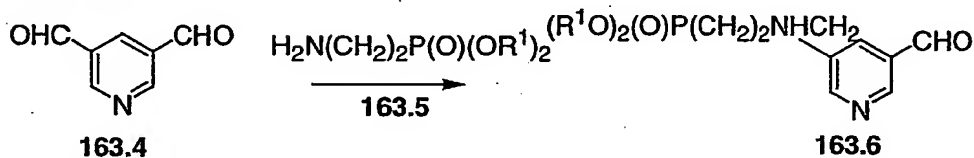
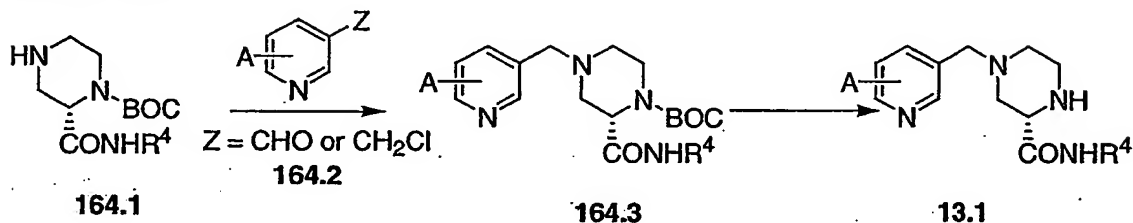


Scheme 161
Method



Example



Scheme 162**Method****Example****Scheme 163****Method****Example****Scheme 164****Preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups.**

- 5 Schemes 165 - 169 illustrate the preparation of dimethoxybenzyl halides 49.7 incorporating phosphonate groups, which are employed in the synthesis of the phosphonate esters 6 and 13.

Scheme 165 depicts the preparation of dimethoxybenzyl alcohols in which the phosphonate group is attached either directly to the phenyl ring or by a saturated or unsaturated alkylene

chain. In this procedure, a bromo-substituted dimethoxy benzyl alcohol is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate 165.2, to afford the coupled product 165.3. The reaction is conducted under the conditions described in Scheme 150. The product 165.3 is then reduced, for example by treatment with diimide, as described in Scheme 150, to yield the saturated analog 165.4. Alternatively, the bromo compound 165.1 is coupled, in the presence of a palladium catalyst, as described in Scheme 144, with a dialkyl phosphite 165.5, to afford the phosphonate 165.6.

For example, 4-bromo-3,5-dimethoxybenzyl alcohol 165.7, the preparation of which is described in J. Med. Chem., 1977, 20, 299, is coupled with a dialkyl allyl phosphonate 165.8 (Aldrich) in the presence of bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product 165.9. The product is reduced, for example by treatment with diimide, as described in J. Org. Chem., 52, 4665, 1987, to yield the saturated compound 165.10.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol 165.7, different benzyl alcohols 165.1, and/or different alkenyl phosphonates 165.2, the corresponding products 165.3 and 165.4 are obtained.

As a further example, 3-bromo-4,5-dimethoxybenzyl alcohol 165.11, the preparation of which is described in J. Org. Chem., 1978, 43, 1580, is coupled, in toluene solution at reflux, with a dialkyl phosphite 165.5, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate 165.12.

Using the above procedures, but employing, in place of the dimethoxy bromobenzyl alcohol 165.11, different benzyl alcohols 165.1, and/or different dialkyl phosphites 165.5, the corresponding products 165.6 are obtained.

Scheme 166 illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted dimethoxybenzyl alcohol 166.1 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 166.2 to prepare the amide 166.3.

For example, 2,6-dimethoxy-4-(hydroxymethyl)benzoic acid 166.4, the preparation of which is described in Chem. Pharm. Bull., 1990, 38, 2118, is coupled in dimethylformamide solution, in

the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate 166.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide 166.6. Using the above procedures, but employing, in place of the dimethoxybenzoic acid 166.4, different benzoic acids 166.1, and/or different aminoalkyl phosphites 166.2, the corresponding products 166.3 are obtained.

Scheme 167 illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an aminoalkyl or an amide group. In this procedure, an amino-substituted dimethoxybenzyl alcohol 167.1 is reacted, under reductive amination conditions, as described in Scheme 163, with a dialkyl formylalkylphosphonate 167.2 to yield the aminoalkyl product 167.3. Alternatively, the amino-substituted dimethoxybenzyl alcohol 167.1 is coupled, as described in Scheme 1, with a dialkyl carboxyalkyl phosphonate 167.4, to produce the amide 167.5.

For example, 3-amino-4,5-dimethoxybenzyl alcohol 167.6, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is reacted, in the presence of sodium triacetoxymethylborohydride, with a dialkyl formylmethyl phosphonate 167.7, as described in Scheme 135, to afford the aminoethyl phosphonate 167.8.

Using the above procedures, but employing, in place of the amine 167.6, different amines 167.1, and/or different formylalkyl phosphites 167.2, the corresponding products 167.3 are obtained.

As a further example, 4-amino-3,5-dimethoxybenzyl alcohol 167.9, the preparation of which is described in Bull. Chem. Soc. Jpn., 1972, 45, 3455, is coupled, in the presence of dicyclohexylcarbodiimide, with a dialkyl phosphonoacetic acid 167.10, (Aldrich) to afford the amide 167.11.

Using the above procedures, but employing, in place of the amine 167.6, different amines 167.1, and/or different carboxyalkyl phosphonates 167.4, the corresponding products 167.5 are obtained.

Scheme 168 illustrates the preparation of dimethoxybenzyl alcohols incorporating phosphonate groups attached by means of an alkoxy group. In this procedure, a dimethoxyhydroxy benzyl alcohol 168.1 is reacted with a dialkyl alkylphosphonate 168.2 with a terminal leaving group to afford the alkoxy product 168.3. The alkylation reaction is

effected in a polar organic solvent such as dimethylformamide in the presence of a base such as dimethylaminopyridine or cesium carbonate.

For example, 4-hydroxy-3,5-dimethoxybenzyl alcohol **168.4**, the preparation of which is described in *J. Med. Chem.* 1999, 43, 3657, is reacted in dimethylformamide at 80°C with an

5 equimolar amount of a dialkyl bromopropyl phosphonate **168.5**, prepared as described in *J. Am. Chem. Soc.*, 2000, 122, 1554, and cesium carbonate, to give the alkylated product **168.6**.

Using the above procedures, but employing, in place of the phenol **168.4**, different phenols **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

10 As a further example, 4,5-dimethoxy-3-hydroxybenzyl alcohol **168.7**, prepared as described in *J. Org. Chem.*, 1989, 54, 4105, is reacted, as described above, with a dialkyl

trifluoromethanesulfonyloxymethyl phosphonate **168.8**, prepared as described in *Tet. Lett.*, 1986, 27, 1477, to produce the alkylated product **168.9**.

Using the above procedures, but employing, in place of the phenol **168.7**, different phenols

15 **168.1**, and/or different alkyl phosphonates **168.2**, the corresponding products **168.3** are obtained.

Scheme 169 illustrates the conversion of the benzyl alcohols **169.1**, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor, prepared as described above, into the

20 corresponding halides **169.2**. The conversion of alcohols into chlorides, bromides and iodides is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 354ff, p. 356ff and p. 358ff. For example, benzyl alcohols are transformed into the

chloro compounds, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in *J. Am. Chem. Soc.*, 106, 3286, 1984. Benzyl alcohols are

25 transformed into bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in *J. Am. Chem. Soc.*, 92, 2139, 1970. Benzyl alcohols are transformed into iodides by reaction with sodium iodide and boron trifluoride etherate, as described in *Tet. Lett.*, 28, 4969, 1987, or by reaction with diphosphorus tetraiodide, as described in *Tet. Lett.*, 1801, 1979. Benzylic chlorides or bromides are transformed into the

30 corresponding iodides by reaction with sodium iodide in acetone or methanol, for example as described in EP 708085.

Preparation of dimethoxythiophenols 23.1 incorporating phosphonate groups.

Schemes 170 - 173 illustrate the preparation of the dimethoxythiophenols 23.1 incorporating phosphonate groups, which are used in the synthesis of the phosphonate esters 6 and 13.

5

Scheme 170 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached by means of an amide group. In this procedure, a dimethoxyamino-substituted benzoic acid 170.1 is converted into the corresponding thiol 170.2. The conversion of amines into the corresponding thiols is described in Sulfur Lett., 10 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol 170.2. The product is then coupled, as described above, with a dialkyl aminoalkyl phosphonate 170.3, to yield the amide 170.4.

15 For example, 5-amino-2,3-dimethoxybenzoic acid 170.5, the preparation of which is described in JP 02028185, is converted, as described above, into 2,3-dimethoxy-5-mercaptobenzoic acid 170.6. The product is then coupled, as described in Scheme 1, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 170.7, (Acros) to afford the amide 170.8.

20 Using the above procedures, but employing, in place of the amine 170.5, different amines 170.1, and/or different aminoalkyl phosphonates 170.3, the corresponding products 170.4 are obtained.

Scheme 171 illustrates the preparation of dimethoxythiophenol derivatives incorporating a 25 phosphonate group attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromodimethoxyaniline 171.1 is converted, as described in Scheme 170, into the corresponding thiophenol 171.2. The thiol group is then protected to give the derivative 171.3. The protection and deprotection of thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277.

30 For example, thiol substituents are protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a chlorotrialkylsilane and a base such as imidazole. Alternatively, thiol substituents are protected by conversion to tert-butyl or

adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The product 171.3 is then coupled, in the presence of a palladium catalyst, as described in Scheme 165, with a dialkyl alkenyl phosphonate 171.4, to give the alkenyl product 171.5. Deprotection then yields the thiol 171.6. Reduction of the double bond, for example by reaction with diimide, as described in J. Org. Chem., 52, 4665, 1987, affords the saturated product 171.7.

For example, 4-bromo-3,5-dimethoxyaniline 171.8, prepared as described in WO9936393, is converted, by diazotization, into 4-bromo-3,5-dimethoxythiophenol 171.9. The product is then transformed into the S-benzoyl derivative 171.10, by reaction with benzoyl chloride in pyridine, and the product is coupled, as described in Scheme 165, with a dialkyl butenyl phosphonate 171.11, the preparation of which is described in J. Med. Chem., 1996, 39, 949, to yield the phosphonate 171.12. Deprotection, for example by treatment with aqueous ammonia at ambient temperature, as described in J. Am. Chem. Soc., 85, 1337, 1963, then afford the thiol 171.13. The double bond is reduced with diimide to give the saturated analog 171.14.

Using the above procedures, but employing, in place of the amine 171.8, different amines 171.1, and/or different alkenyl phosphonates 171.4, the corresponding products 171.6 and 171.7 are obtained.

Scheme 172 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group directly attached to the phenyl ring. In this procedure, a protected bromodimethoxythiophenol 172.1, prepared, for example, from the corresponding aniline, as described above, is coupled, in the presence of a palladium catalyst, as described in Scheme 165, with a dialkyl phosphite 172.2. The product is then deprotected to afford the phosphonate ester 172.4.

For example, 3-bromo-4,5-dimethoxyaniline 172.5, prepared as described in DE 2355394, is converted, as described above in Schemes 165 and 171, into S-benzoyl 3-bromo-4,5-dimethoxythiophenol 172.6. This compound is then coupled, in toluene solution at reflux, with a dialkyl phosphite 172.2, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to yield the phenyl phosphonate 172.7.

Deprotection, as described in Scheme 171, then affords the thiol 172.8.

Using the above procedures, but employing, in place of the protected thiol 172.6, different thiol 172.1, the corresponding products 172.4 are obtained.

Scheme 173 illustrates the preparation of dimethoxythiophenol derivatives incorporating a phosphonate group attached to the phenyl ring by means of an alkoxy group. In this procedure, a dimethoxy aminophenol 173.1 is converted, via the diazo compound, into the corresponding thiophenol 173.2. The thiol group is then protected, and the product 173.3 is alkylated, as described in Scheme 168, with a dialkyl bromoalkyl phosphonate 173.4. Deprotection of the product 173.5 then affords the thiophenol 173.6.

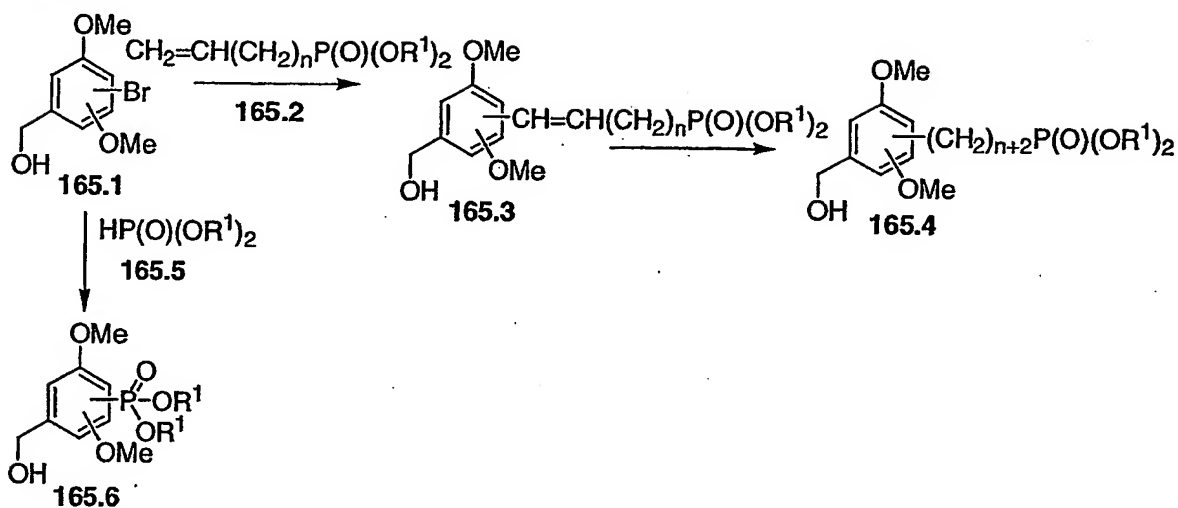
- 10 For example, 5-amino-2,3-dimethoxyphenol 173.7, prepared as described in WO 9841512, is converted by diazotization, as described above, into the thiophenol 173.8, and the product is protected by reaction with one molar equivalent of benzoyl chloride in pyridine, to yield the S-benzoyl product 173.9. The latter compound is then reacted, in dimethylformamide solution at 80°C, with a dialkyl bromoethyl phosphonate 173.10 (Aldrich) and cesium carbonate, to
- 15 produce the ethoxyphosphonate 173.11. Deprotection, as described in Scheme 171, then yields the thiol 173.12.

Using the above procedures, but employing, in place of the thiol 173.8, different thiol 173.2, and/or different bromoalkyl phosphonates 173.4, the corresponding products 173.6 are obtained.

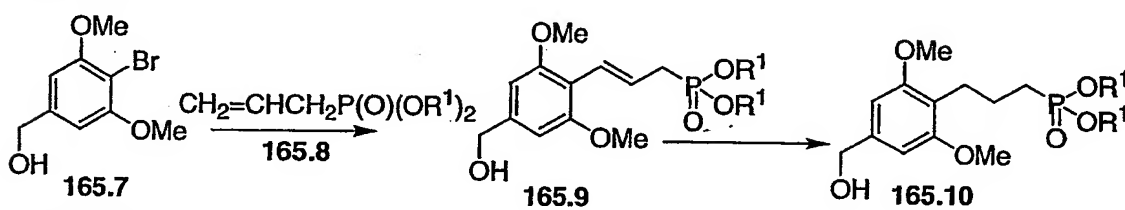
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Scheme 165

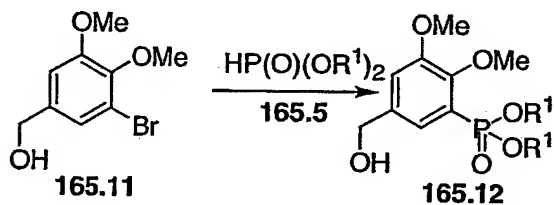
Method



Example 1

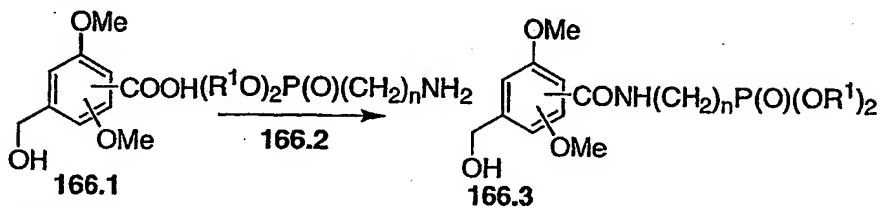


Example 2

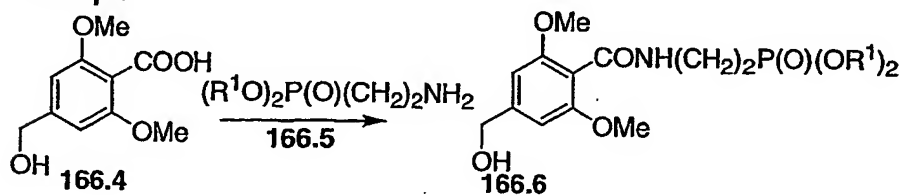


Scheme 166

Method

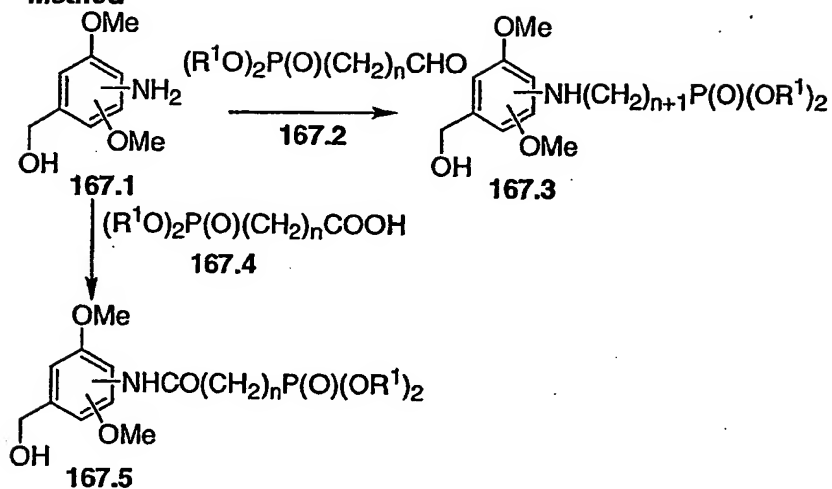


Example

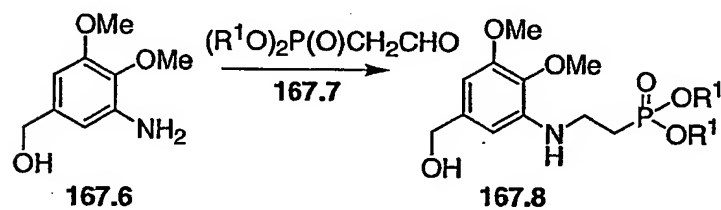


Scheme 167

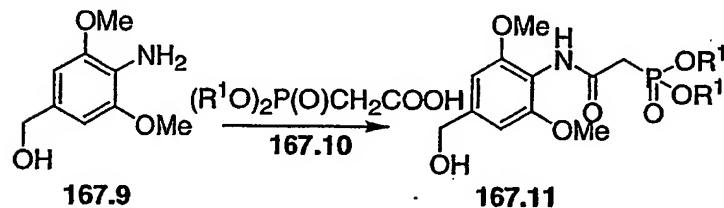
Method



Example 1

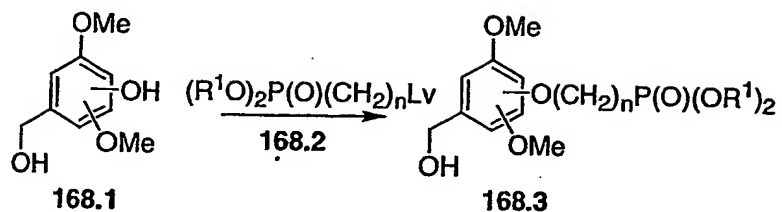


Example 2

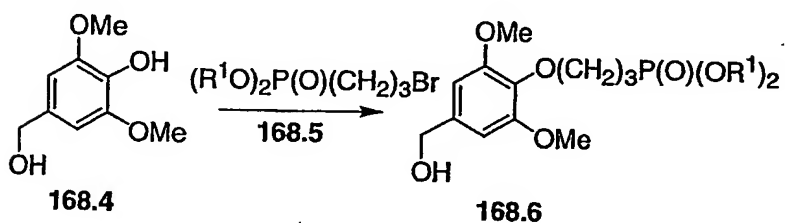


Scheme 168

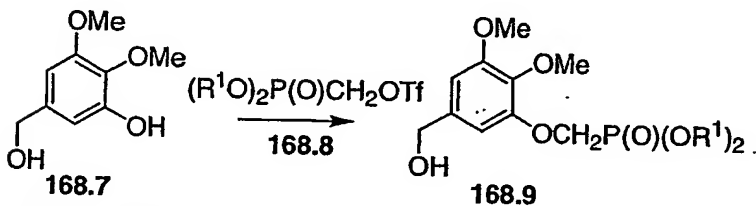
Method



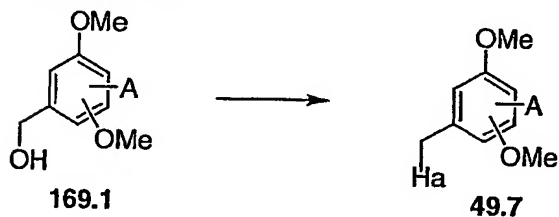
Example 1



Example 2

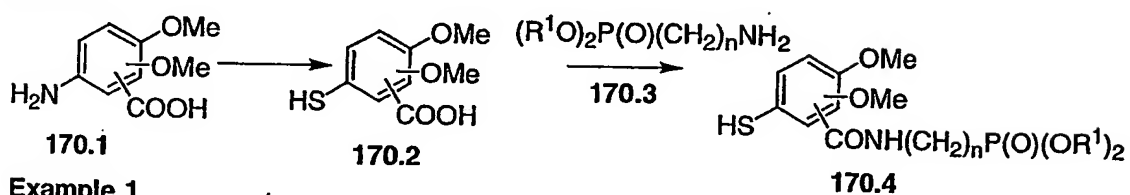


Scheme 169

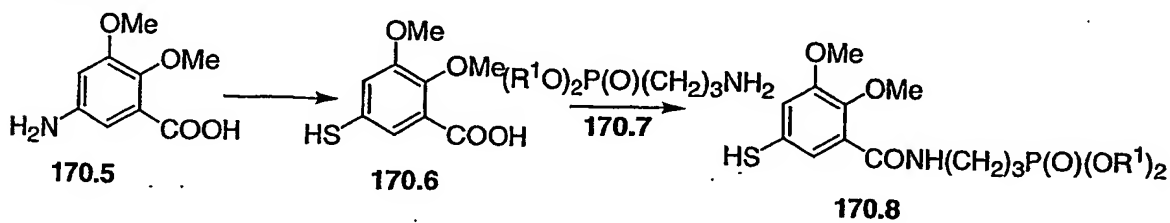


Scheme 170

Method

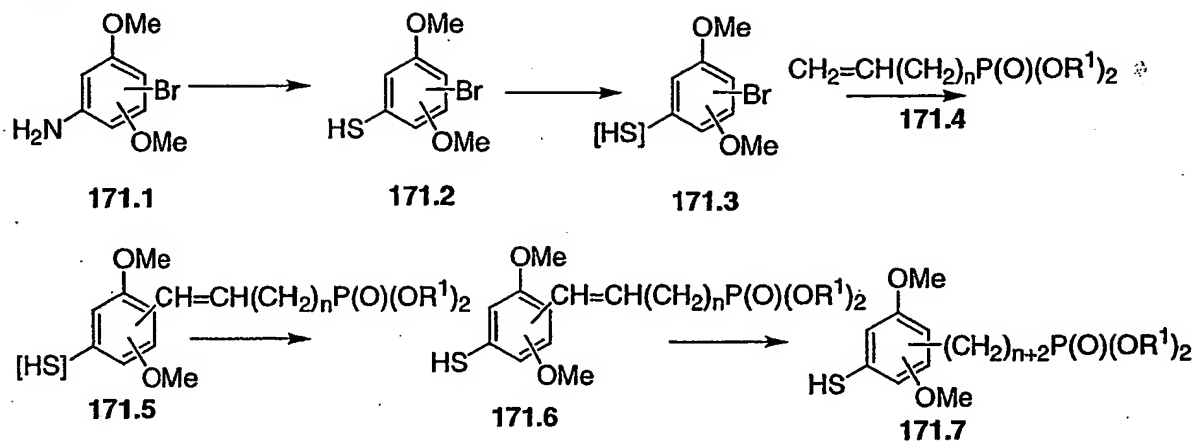


Example 1

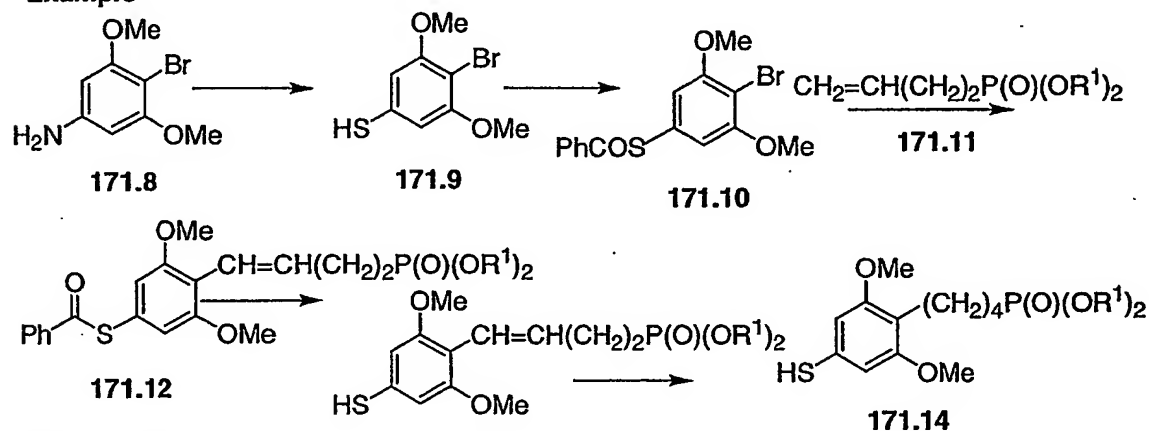


Scheme 171

Method

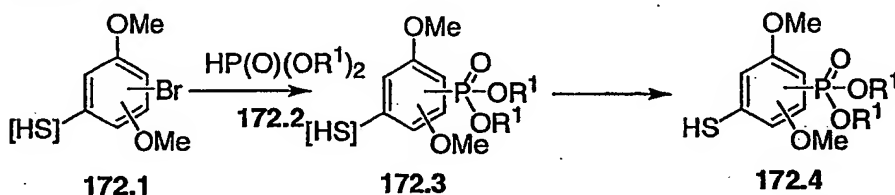


Example

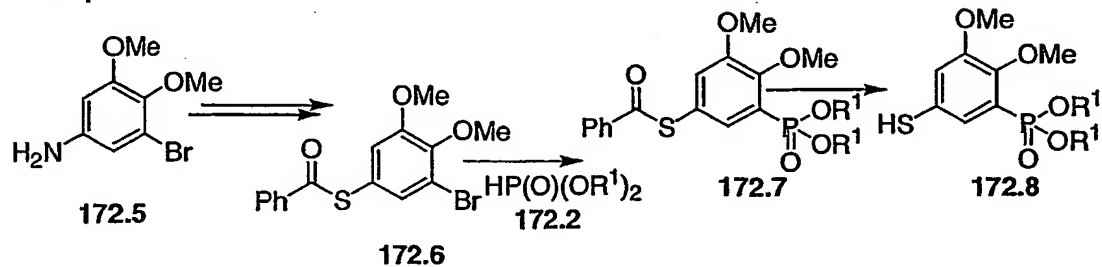


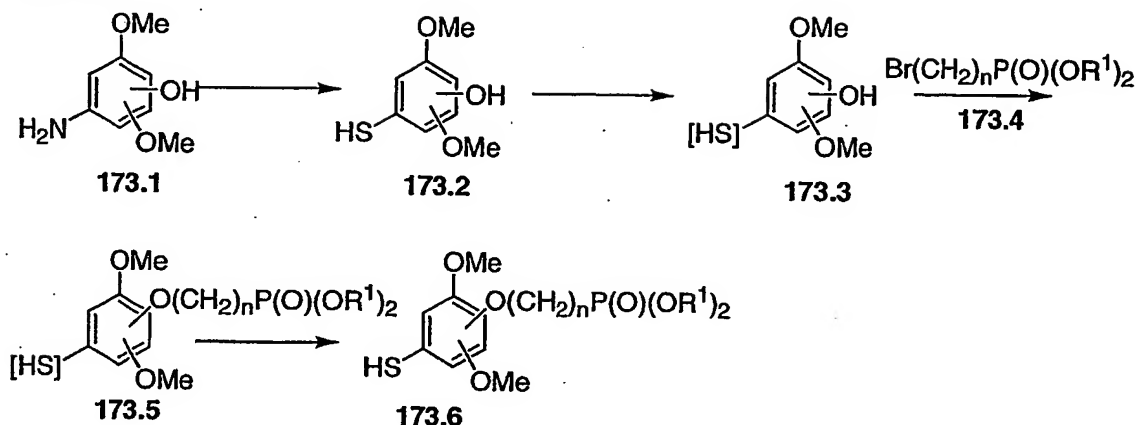
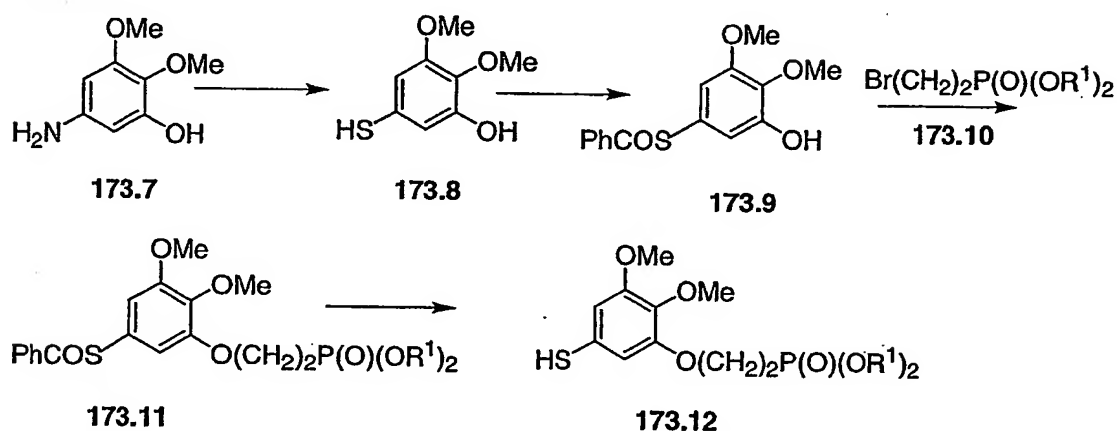
Scheme 172

Method



Example



Scheme 173**Method****Example**

5 Preparation of ethanolamine derivatives 29.1 incorporating phosphonate groups.

Schemes 174 - 178 illustrate the preparation of the ethanolamine derivatives 29.1 which are employed in the preparation of the phosphonate esters 18 and 8.

- 10 Scheme 174 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkyl chain. In this procedure, ethanolamine 174.1 is protected to give the derivative 174.2. The product is then reacted with a dialkyl alkyl phosphonate 174.3 in which the alkyl group incorporates a leaving group Lv. The alkylation

reaction is performed in a polar organic solvent such as acetonitrile or dimethylformamide, in the presence of a strong base such as sodium hydride or lithium hexamethyldisilazide, to afford the ether product 174.4. The protecting group is then removed to yield the amine 174.5. The protection and deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309. The amino compound 174.5 is then coupled, as described in Scheme 1, with the aminoacid 174.6, to give the amide 174.7.

For example, equimolar amounts of phthalimide and ethanolamine are reacted in toluene at 70°C, as described in J. Org. Chem., 43, 2320, 1978, to prepare the phthalimido derivative 174.8, in which Phth is phthalimido. The product is then reacted, in tetrahydrofuran, with sodium hydride and an equimolar amount of a dialkyl trifluoromethylsulfonyloxymethyl phosphonate 174.9, the preparation of which is described in Tet. Lett., 1986, 27, 1497, to afford the ether product 174.10. The phthalimido group is then removed by treatment of the product 174.10 with ethanolic hydrazine at ambient temperature, as described in J. Org. Chem., 43, 2320, 1978, to yield the amine 174.11. The product is then coupled, in the presence of dicyclohexylcarbodiimide, with the aminoacid 174.6, to yield the amide 174.12. Using the above procedures, but employing, in place of the methylphosphonate 174.9, different alkylphosphonates 174.3, the corresponding products 174.7 are obtained.

Scheme 175 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain incorporating a nitrogen. In this procedure, ethanolamine 174.1 and the aminoacid 174.6 are coupled, as described in Scheme 1, to form the amide 175.1. The product is then alkylated with a bromoalkyl aldehyde 175.2 to yield the ether 175.3. The alkylation reaction is performed in a polar organic solvent such as acetonitrile or dioxan, in the presence of a strong base such as potassium tert. butoxide or sodium hydride, at about 60°C. The aldehyde product is then reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate 175.4, to produce the amine product 175.5.

For example, the amide 175.1 is reacted, as described above, with bromoacetaldehyde 175.6, to afford the ether 175.7. The product is then reacted in ethanol with a dialkyl aminoethyl phosphonate 175.8, (Aurora) and sodium triacetoxyborohydride, to yield the amine 175.9.

Using the above procedures, but employing, in place of the bromoacetaldehyde 175.6, different bromoalkyl aldehydes 175.2, and/or different aminoalkyl phosphonates 175.4, the corresponding products 175.5 are obtained.

- 5 Scheme 176 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of a phenyl ring. In this procedure, bromoethylamine 176.1 and the aminoacid 174.6 are coupled, as described in Scheme 1, to afford the amide 176.2. The product is then reacted with the dialkyl hydroxyalkyl-substituted phenylphosphonate 176.3 to prepare the ether 176.4. The alkylation reaction is performed in a polar organic solvent such as dimethyl sulfoxide or dioxan, in the presence of a base such as lithium
- 10 bis(trimethylsilyl)amide, sodium hydride or lithium piperidide.
- For example, the amide 176.2 is reacted in dimethylformamide with a dialkyl 4-(2-hydroxyethyl)phenyl phosphonate 176.5, prepared as described in J. Am. Chem. Soc., 1996, 118, 5881, and sodium hydride, to furnish the ether product 176.6.
- 15 Using the above procedures, but employing, in place of the hydroxyethyl phenylphosphonate 176.5, different phosphonates 176.3, the corresponding products 176.4 are obtained.

Scheme 177 illustrates the preparation of ethanolamine derivatives in which the phosphonate group is attached by means of an alkylene chain. In this procedure, the aminoacid 174.6 is

20 coupled with a bromoalkoxy-substituted ethylamine 177.1 to give the amide 177.2. The product is then subjected to an Arbuzov reaction with a trialkyl phosphite $P(OR^1)_3$. In this procedure, described in Handb. Organophosphorus Chem., 1992, 115, the reactants are heated together at ca. 100°C to afford the product 177.4.

For example, the aminoacid 174.6 is coupled, as described in Scheme 1, in acetonitrile solution containing dicyclohexylcarbodiimide, with 2-bromoethoxyethylamine 177.5, prepared as

25 described in Vop. Khim. Tekh., 1974, 34, 6, to produce the amide 177.6. The product is then heated at 120°C with excess trialkyl phosphite 177.3, to afford the phosphonate 177.7.

Using the above procedures, but employing, in place of the bromoethoxyethylamine 177.5, different bromoalkyl ethylamines 177.1, the corresponding products 177.4 are obtained.

30

Scheme 178 depicts the preparation of the amines 29.1. The BOC-protected ethanolamine derivatives 178.1, in which the group A is either the substituent link- $P(O)(OR^1)_2$, or a

precursor thereto, prepared as described in Schemes 174 - 177, are deprotected to afford the amines 29.1. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection is effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride in ethyl acetate, or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preparation of the chroman phosphonate esters 33.1.

Schemes 179 - 181a illustrate the preparation of the chroman phosphonate esters 33.1 which are employed in the preparation of the phosphonate esters 17 and 9.

Scheme 179 depicts the preparation of (2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazol-4-yl)-methanol, 179.6, 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carbaldehyde, 179.7, and 2-methyl-3a,9b-dihydro-4H-chromeno[4,3-d]oxazole-4-carboxylic acid, 179.8, which are used in the preparation of the phosphonates 33.1. In this procedure, (2H-chromen-2-yl)-methanol 179.1, prepared as described in J. Chem. Soc., (D), 344, 1973, is converted, as described above, (Scheme 1) into the tert. butyldimethylsilyl ether 179.2. The product is then reacted, as described in J. Het. Chem., 1975, 12, 1179, with silver cyanate and iodine in ether, so as to afford the addition product 179.3. This compound is then heated on methanol to yield the carbamate derivative 179.4. The latter compound is heated in xylene at reflux, as described in J. Het. Chem., 1975, 12, 1179, to produce the oxazoline derivative 179.5. The silyl group is then removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran to yield the carbinol 179.6. The carbinol is oxidized to produce the aldehyde 179.7. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, dimethyl sulfoxide/acetic anhydride or dimethyl sulfoxide-dicyclohexyl carbodiimide. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. The aldehyde 179.7 is oxidized to the carboxylic acid 179.8. The oxidation of aldehydes to carboxylic acids is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 838ff. The conversion is effected by treatment with oxidizing agents such as potassium permanganate,

ruthenium tetroxide, chromium trioxide in acetic acid, or, preferably, by the use of silver oxide, as described in J. Am. Chem. Soc., 73, 2590, 1951.

Scheme 180 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde 179.7 is reacted, under reductive amination conditions, as described in Scheme 175, with a dialkyl aminoalkyl phosphonate 180.1, to give the amine 180.2. The oxazoline group is then hydrolyzed, for example by reaction with aqueous potassium hydroxide, as described in J. Het. Chem., 1975, 12, 1179, to yield the hydroxyamine 180.3.

For example, the aldehyde 179.7 is reacted in ethanol with a dialkyl aminomethyl phosphonate 180.4, (Interchim) and sodium triacetoxyborohydride, to produce the amine 180.5. The oxazoline is then hydrolyzed, as described above, to afford the hydroxyamine 180.6. Using the above procedures, but employing, in place of the aminomethyl phosphonate 180.4, different phosphonates 180.1, the corresponding products 180.3 are obtained.

Scheme 181 illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of an amide group. In this procedure, the carboxylic acid 179.8 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 180.1, to produce the amide 181.1. Hydrolysis of the oxazoline group, as described above, then yields the hydroxyamine 181.2.

For example, the carboxylic acid 179.8 is coupled with a dialkyl aminopropyl phosphonate 181.3, (Acros) to afford the amide 181.4, which is then hydrolyzed to give the hydroxyamine 181.5.

Using the above procedures, but employing, in place of the aminopropyl phosphonate 181.3, different phosphonates 180.1, the corresponding products 181.2 are obtained.

Scheme 181a illustrates the preparation of chroman derivatives in which the phosphonate group is attached by means of a thioalkyl group. In this procedure, the carbinol 179.6 is converted into the bromo derivative 181a.1. The conversion of alcohols into bromides is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 356ff. For example, the alcohol is reacted with triphenyl phosphine and carbon tetrabromide, trimethylsilyl bromide, thionyl bromide and the like. The bromo compound is

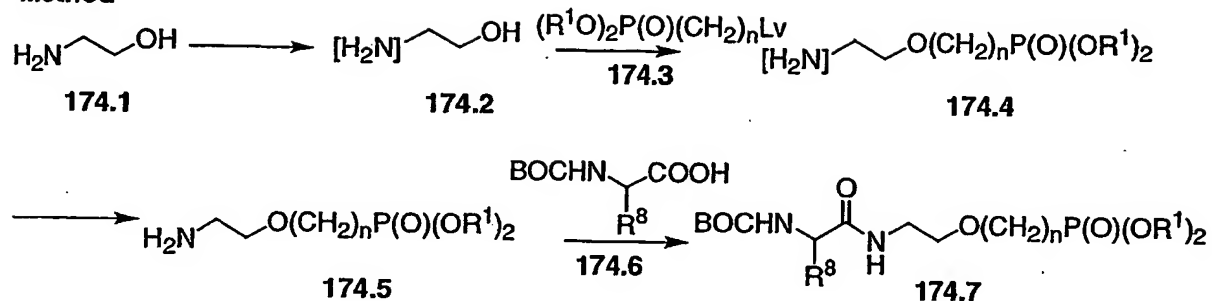
then reacted with a dialkyl thioalkyl phosphonate **181a.2** to effect displacement of the bromide and formation of the thioether **181a.3**. The reaction is performed in a polar organic solvent such as ethanol in the presence of a base such as potassium carbonate. Removal of the isoxazoline group then produces the hydroxyamine **181a.4**.

- 5 For example, the bromo compound **181a.1** is reacted in ethanol with a dialkyl thioethyl phosphonate **181a.5**, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to yield the thioether product **181a.6**. Hydrolysis, as described above, then affords the hydroxyamine **181a.7**.

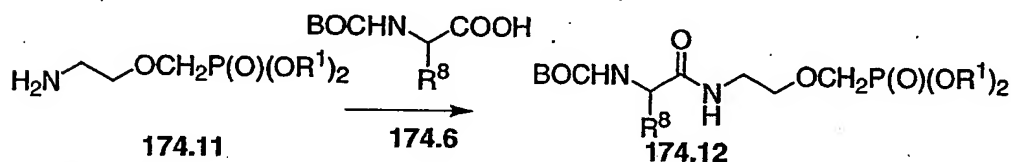
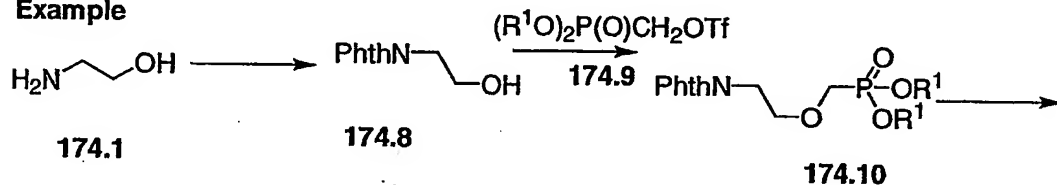
- 10 Using the above procedures, but employing, in place of the thioethyl phosphonate **181a.5**, different phosphonates **181a.2**, the corresponding products **181a.4** are obtained.

Scheme 174

Method

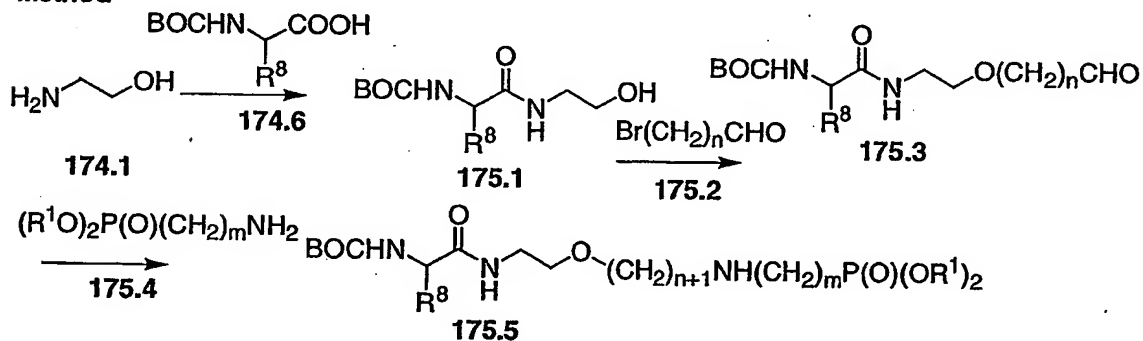


Example

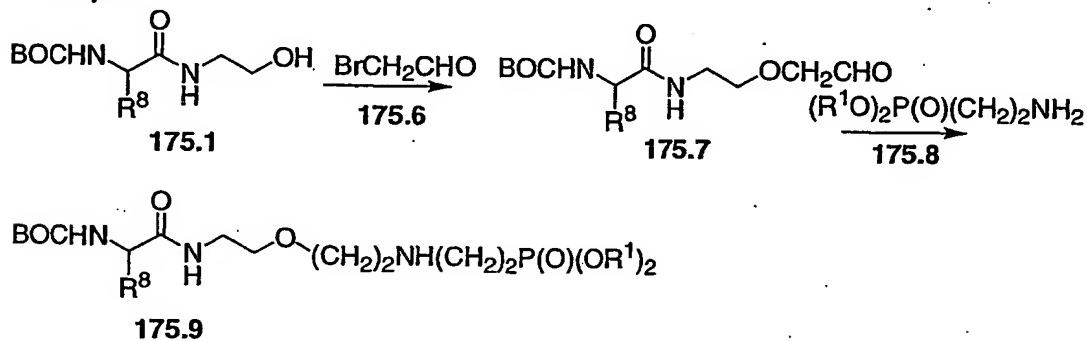


Scheme 175

Method

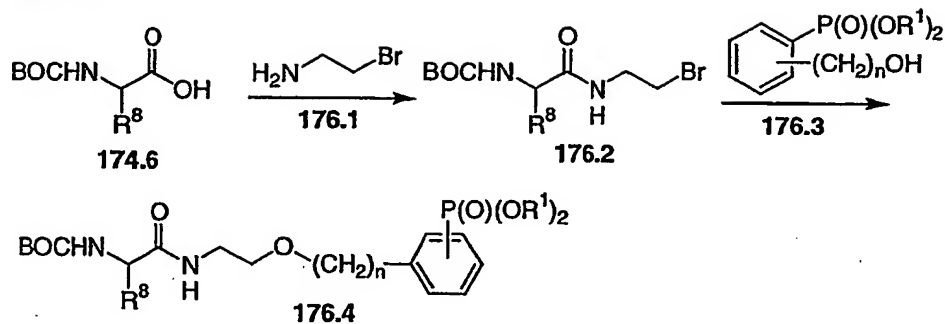


Example

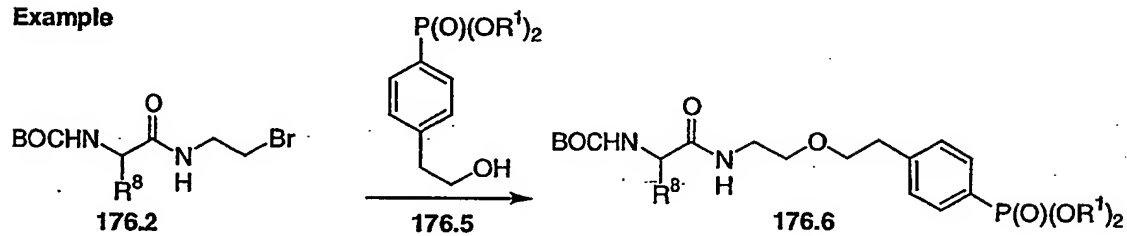


Scheme 176

Method

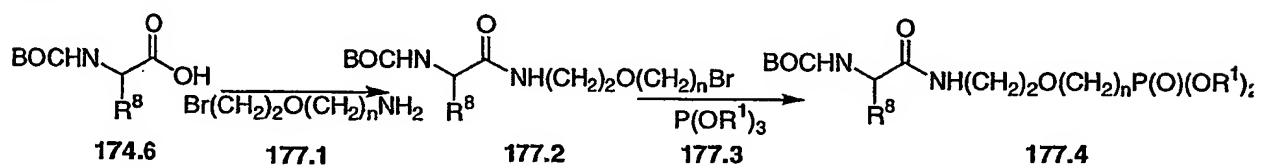


Example

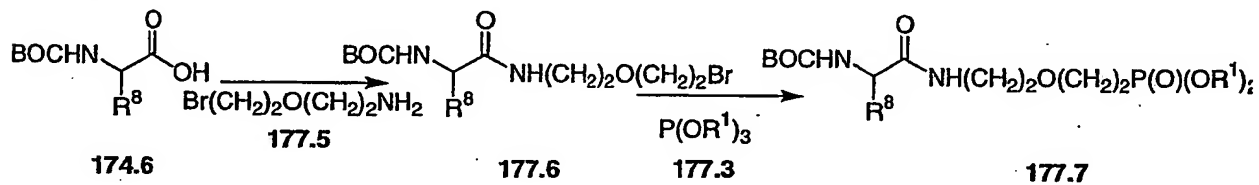


Scheme 177

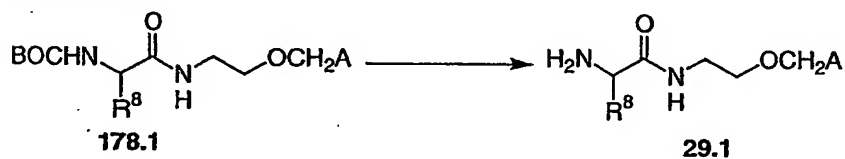
Method



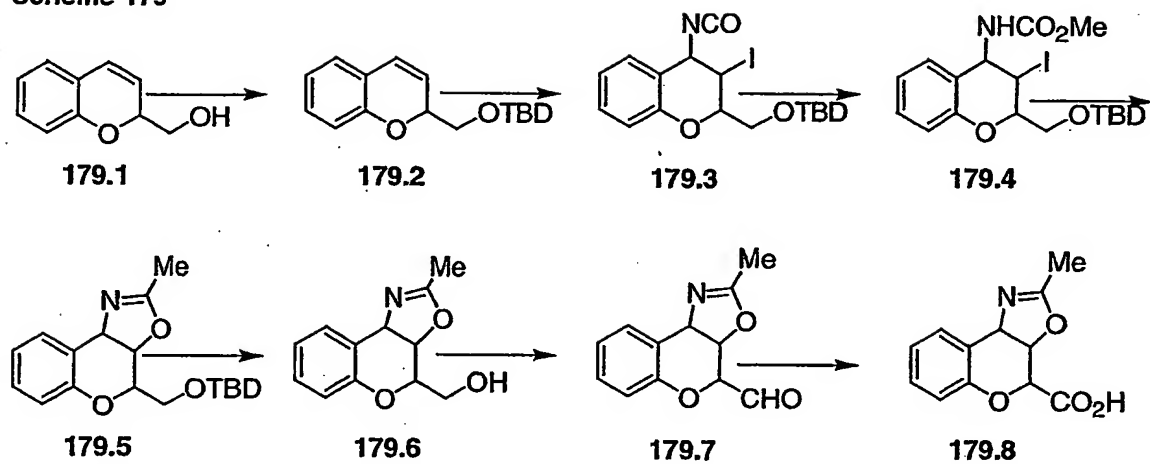
Example



Scheme 178

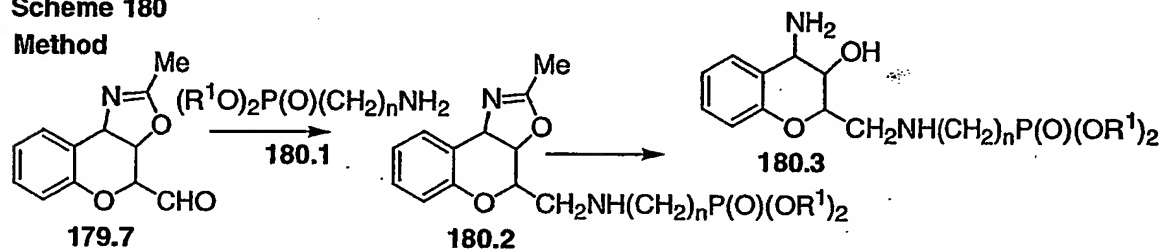


Scheme 179

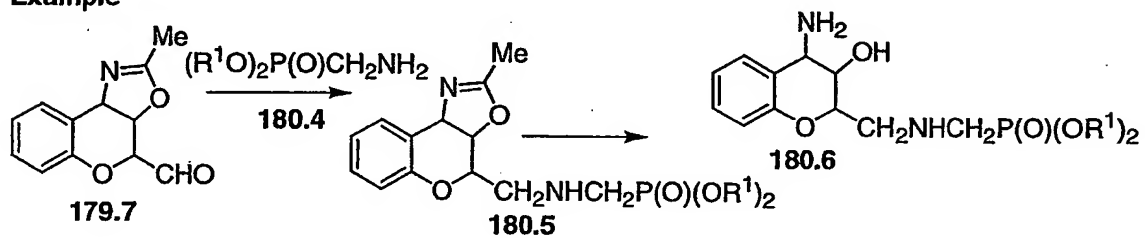


Scheme 180

Method

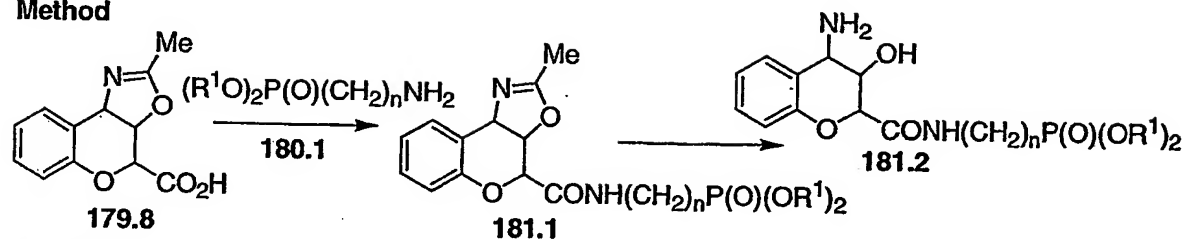


Example

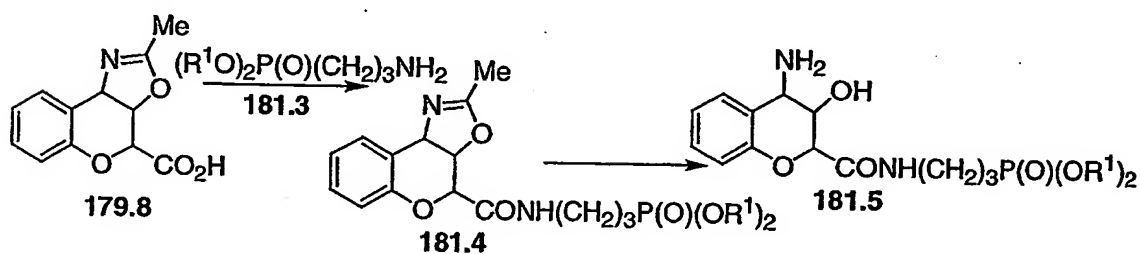


Scheme 181

Method

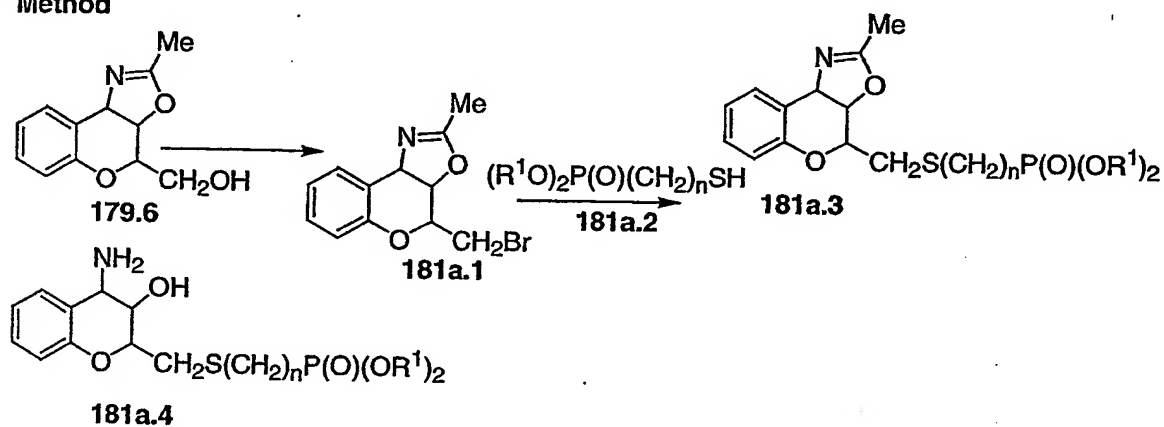


Example

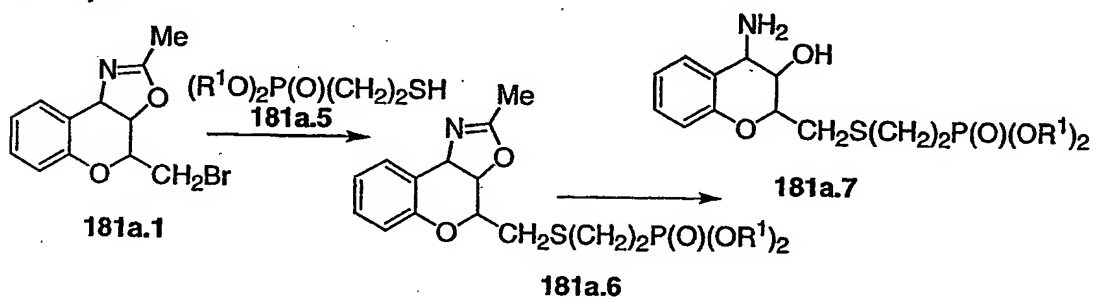


Scheme 181a

Method



Example



Preparation of phenylalanine derivatives 37.1 incorporating phosphonate moieties.

Schemes 182 - 185 illustrate the preparation of phosphonate-containing phenylalanine derivatives 37.1 which are employed in the preparation of the intermediate phosphonate esters 10 and 19.

5

Scheme 182 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 182.1.

- 10 In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 182.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion is effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a
- 15 benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 182.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-
- 20 butyldiphenylsilyl. Thiophenols are also protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. The protected hydroxy- or mercapto ester 182.3 is then converted into the BOC derivative 182.4. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic
- 25 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups are removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.
- 30 The resultant phenol or thiophenol 182.5 is then reacted under various conditions to provide protected phenylalanine derivatives 182.9, 182.10 or 182.11, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol 182.5 is reacted with a dialkyl bromoalkyl phosphonate 182.6 to afford the ether or thioether product 182.9. The alkylation reaction is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°C, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product 182.9. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid 182.12. The benzyl esters 182.10 and 182.11, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme 182, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, 182.13 is converted, as described above, into the benzyl ester 182.14. The latter compound is then reacted with one molar equivalent of chloro tert-butyldimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether 182.15. This compound is then converted, as described above, into the BOC derivative 182.16. The silyl protecting group is removed by treatment of the silyl ether 182.16 with a tetrahydrofuran solution of tetrabutylammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 182.17. The latter compound is then reacted in dimethylformamide at ca. 60°C, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 182.18 (Aldrich), in the presence of cesium carbonate, to afford the alkylated product 182.19. Debenzylation then produces the carboxylic acid 182.20.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 182.13, different hydroxy or thio-substituted phenylalanine derivatives 182.1, and/or different bromoalkyl phosphonates 182.6, the corresponding ether or thioether products

182.12 are obtained.

Alternatively, the hydroxy or mercapto-substituted phenylalanine derivative 182.5 is reacted with a dialkyl hydroxymethyl phosphonate 182.7 under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds 182.10. The preparation of aromatic ethers and thioethers by means of the Mitsunobu reaction is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic

solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products **182.10**.

For example, as shown in Scheme **182**, Example 2, 3-mercaptophenylalanine **182.21**, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester **182.22**.

- 5 The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether **182.23**. This compound is then converted into the BOC-protected derivative **182.24**. The 4-methoxybenzyl group is then removed by the reaction of the thioether **182.24** with mercuric trifluoroacetate and anisole in
- 10 trifluoroacetic acid, as described in J. Org. Chem., 52, 4420, 1987, to afford the thiol **182.25**. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate **182.7**, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product **182.26**. The benzyl ester protecting group is then removed to afford the carboxylic acid **182.27**.
- 15 Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative **182.21**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or different dialkyl hydroxymethyl phosphonates **182.7**, the corresponding products **182.10** are obtained.

- Alternatively, the hydroxy or mercapto-substituted protected phenylalanine derivative **182.5** is
- 20 reacted with an activated derivative of a dialkyl hydroxymethylphosphonate **182.8** in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products **182.11**.

- For example, as illustrated in Scheme **182**, Example 3, 3-hydroxyphenylalanine **182.28** (Fluka)
- 25 is converted, using the procedures described above, into the protected compound **182.29**. The latter compound is reacted, in dimethylformamide at ca. 50°C, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate **182.30**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product **182.31**. Debenzylation then produces the carboxylic acid **182.32**.

- 30 Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative **182.28**, different hydroxy or mercapto-substituted phenylalanines **182.1**, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates **182.8**, the corresponding products **182.11** are obtained.

Scheme **183** illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted protected phenylalanine derivative **183.3** and a dialkyl aminoalkylphosphonate **183.4**.

In this procedure, a hydroxymethyl-substituted phenylalanine **183.1** is converted, as described above, into the BOC protected benzyl ester **183.2**. The latter compound is then oxidized to afford the corresponding aldehyde **183.3**. The conversion of alcohols to aldehydes is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product **183.3**. For example, the carbinol **183.2** is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the aldehyde **183.3**. This compound is reacted with a dialkyl aminoalkylphosphonate **183.4** in the presence of a suitable reducing agent to afford the amine product **183.5**. The preparation of amines by means of reductive amination procedures is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid **183.6**.

For example, 3-(hydroxymethyl)-phenylalanine **183.7**, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated derivative **183.8**. This compound is then reacted with a dialkyl aminoethylphosphonate **183.9**, prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product **183.10**, which is then deprotected to give the carboxylic acid **183.11**.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 183.7, different hydroxymethyl phenylalanines 183.1, and/or different aminoalkyl phosphonates 183.4, the corresponding products 183.6 are obtained.

5 Scheme 184 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 184.1 is converted, as described above, (Scheme 182) into the protected derivative 184.2. The product is then coupled, in the presence of a palladium(0) catalyst, with
10 arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid 184.5.

For example, 3-bromophenylalanine 184.6, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 182) into the protected compound 184.7. This
15 compound is then reacted, in toluene solution at reflux, with diethyl phosphite 184.8, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 184.9. Debenzylation then yields the carboxylic acid 184.10.

Using the above procedures, but employing, in place of 3-bromophenylalanine 184.6, different
20 bromophenylalanines 184.1, and/or different dialkylphosphites 184.3, the corresponding products 184.5 are obtained.

Scheme 185 depicts the preparation of the aminoacid derivative 37.1 which is employed in the preparation of the phosphonate esters 10 and 19. In this procedure, the BOC-protected
25 phenylalanine derivatives 185.1, in which the substituent A is the group link-P(O)(OR¹)₂ or a precursor group, the preparation of which is described in Schemes 182 – 184, is converted into the esters or amides 185.2 in which R⁹ is morpholino or alkoxy. The transformation is accomplished by coupling the acid, as described in Scheme 1, with morpholine or an alkanol in the presence of a carbodiimide. The product 185.2 is then deprotected to afford the free
30 amine 185.3, for example as described in Scheme 3. The amine 185.3 is then coupled, as described in Scheme 1, with the aminoacid 174.6, to give the amide 185.4. The BOC group is then removed, as described in Scheme 49, to produce the amine 37.1.

Preparation of the dimethoxyphenylpropionic esters 21.1 incorporating phosphonate groups.

Scheme 186 illustrates the preparation of the dimethoxyphenylpropionic acid derivatives 21.1 which are employed in the preparation of the phosphonate esters 6. In this procedure, the dimethoxybenzyl alcohol derivative 186.1, in which the substituent A is the group link- $P(O)(OR^1)_2$ or a precursor group, the preparation of which is described in Schemes 165 – 168, is converted into the corresponding aldehyde 186.2. The oxidation is effected as described in Scheme 175. The aldehyde is then subjected to a Wittig reaction with methyl triphenylphosphoranylideneacetate 138.2, as described in Scheme 138, to generate the cinnamic ester derivative 186.3. The double bond is then reduced, as described in Scheme 138, to afford the phenylpropionic ester 21.1. Alternatively, the dimethoxybenzyl bromide derivative 186.4, the preparation of which is described in Scheme 169, is reacted, as described in Scheme 138, with dimethyl malonate 186.5 to yield the malonic ester derivative 186.6, which is then transformed, as described in Scheme 138, into the ester 21.1.

Preparation of the phosphonate-containing benzyl iodides 58.1 and benzylcarbamates 125.3.

Schemes 187 - 191 illustrate methods for the preparation of the benzyl iodide derivatives 58.1 which are employed in the synthesis of the phosphonate esters 14, and of the benzyl carbamates 125.3 which are employed in the preparation of the phosphonate esters 22.

Scheme 187 illustrates the preparation of benzaldehyde phosphonates 187.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 187.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 187.2, under reductive amination conditions, as describe above in Scheme 135, to yield the phosphonate product 187.3.

For example, benzene-1,3-dialdehyde 187.4 is reacted with a dialkyl aminopropyl phosphonate 187.5, (Acros) and sodium triacetoxymethylborohydride, to afford the product 187.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 187.4, different benzene dialdehydes 187.1, and/or different phosphonates 187.2, the corresponding products 187.3 are obtained.

- 5 Scheme 188 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde 188.1 is coupled, under palladium catalysis as described in Scheme 150, with a dialkyl alkenylphosphonate 188.2, to afford the alkenyl phosphonate 188.3. Optionally, the product is reduced, as described in Scheme 150, to afford the saturated
- 10 phosphonate ester 188.4. Alternatively, the bromobenzaldehyde is coupled, as described in Scheme 144, with a dialkyl phosphite 188.5 to afford the formylphenylphosphonate 188.6. For example, as shown in Example 1, 3-bromobenzaldehyde 188.7 is coupled with a dialkyl propenylphosphonate 188.8 (Aldrich) to afford the propenyl product 188.9. Optionally, the product is reduced, as described in Scheme 150, to yield the propyl phosphonate 188.10.
- 15 Using the above procedures, but employing, in place of 3-bromobenzaldehyde 188.7, different bromobenzaldehydes 188.1, and/or different alkenyl phosphonates 188.2, the corresponding products 188.3 and 188.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde 188.11 is coupled, as described in Scheme 144, with a dialkyl phosphite 188.5 to afford the 4-formylphenyl phosphonate

20 product 188.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 188.11, different bromobenzaldehydes 188.1, the corresponding products 188.6 are obtained.

- Scheme 189 illustrates the preparation of formylphenyl phosphonates in which the
- 25 phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine 189.1 is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate 189.2, to afford the phenoxy, phenylthio or phenylamino phosphonate product 189.3. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or
- 30 acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 189.1. In cases in which Y is O, a strong base such as sodium hydride or lithium

hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol **189.4**, prepared as described in *Macromolecules*, 1991, 24, 1710, is reacted in acetonitrile at 60°C with one molar equivalent of a dialkyl

5 iodomethyl phosphonate **189.5**, (Lancaster) to give the ether product **189.6**.

Using the above procedures, but employing, in place of the carbinol **189.4**, different carbinols, thiols or amines **189.1**, and/or different haloalkyl phosphonates **189.2**, the corresponding products **189.3** are obtained.

10 Scheme **190** illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid **190.1** is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, **190.2**, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to

15 afford diaryl compounds is described in *Palladium Reagents and Catalysts*, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product **190.3** is then coupled, as described above (Scheme **144**) with a dialkyl phosphite **190.4** to afford the phosphonate **190.5**.

20 For example, 4-formylbenzeneboronic acid **190.6** is coupled with 2,5-dibromothiophene **190.7** to yield the phenylthiophene product **190.8**. This compound is then coupled with the dialkyl phosphite **190.4** to afford the thienyl phosphonate **190.9**.

Using the above procedures, but employing, in place of dibromothiophene **190.7**, different dibromoarenes **190.2**, and/or different formylphenyl boronates **190.1**, the corresponding

25 products **190.5** are obtained.

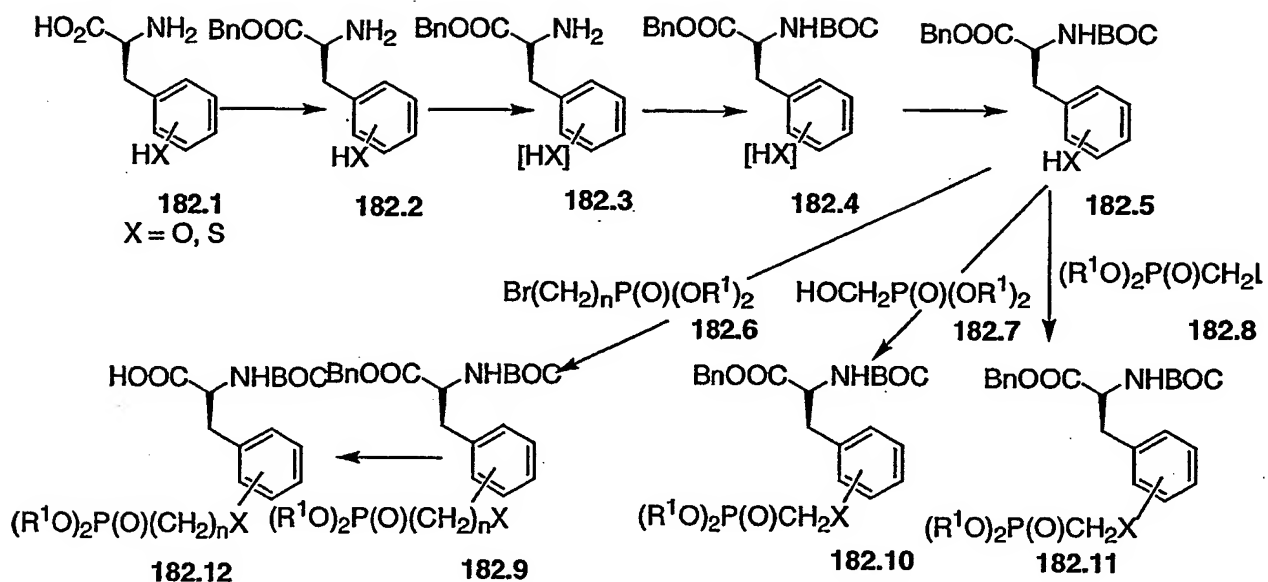
Scheme **191** illustrates the preparation of the benzyl carbamates **125.3** and the benzyl iodides **58.1**, which are employed respectively in the preparation of the phosphonate esters **22** and **4**. In this procedure, the substituted benzaldehydes **191.1**, prepared as shown in Schemes **187** –

30 **190**, are converted into the corresponding benzyl alcohols **191.2**. The reduction of aldehydes to afford alcohols is described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the use of reducing agents such as

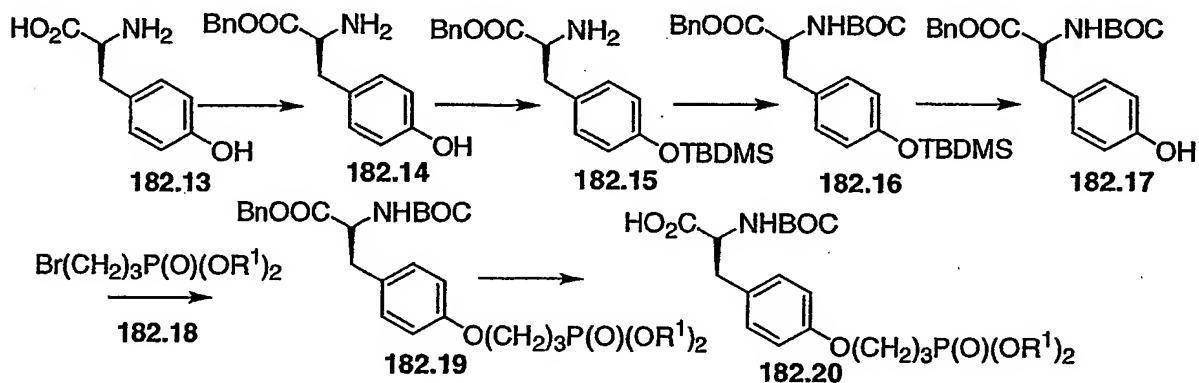
sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **191.3** to afford the carbamate **191.4**. The reaction is performed under the conditions described below, Scheme **198**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce
5 an intermediate benzyloxycarbonyl imidazole, and the intermediate is reacted with the aminoester **191.3** to afford the carbamate **191.4**. The methyl ester is then hydrolyzed, as described in Scheme **3**, to yield the carboxylic acid **125.3**. Alternatively, the benzyl alcohol **191.2** is converted, using the procedures of Scheme **169**, into the iodide **58.1**.

Scheme 182

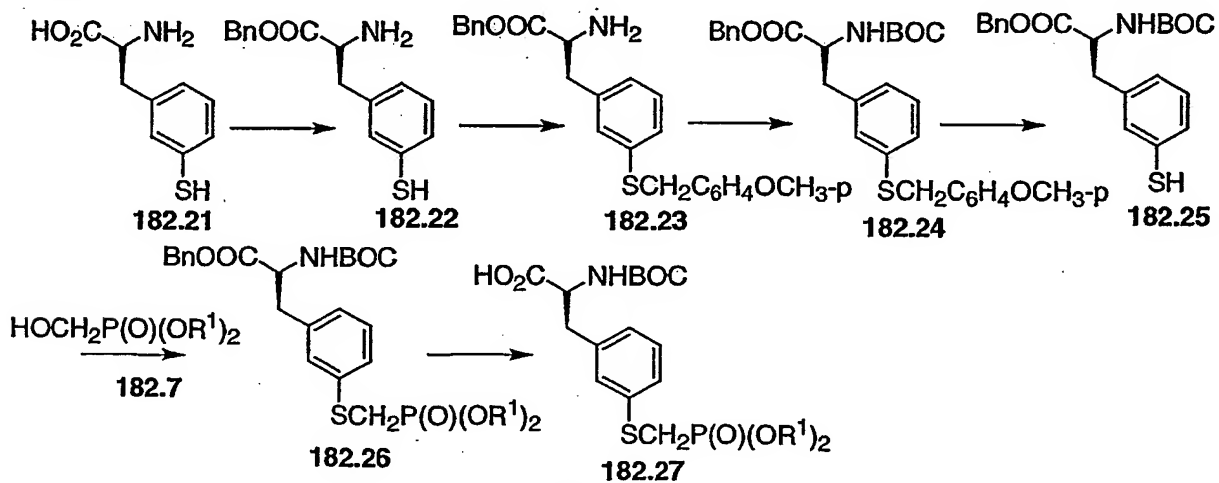
Method



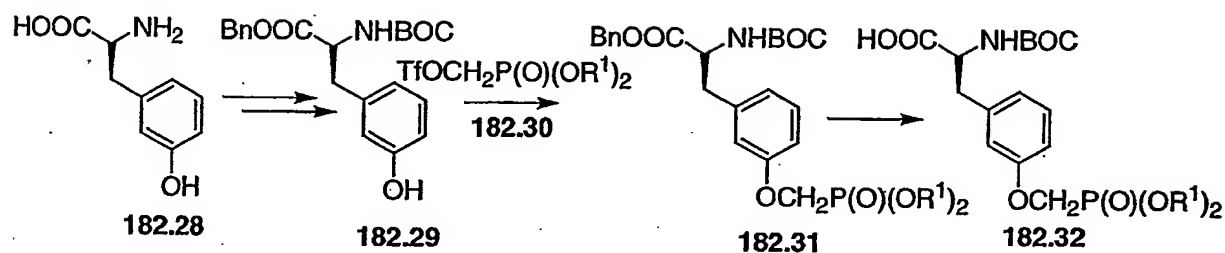
Example 1



Example 2

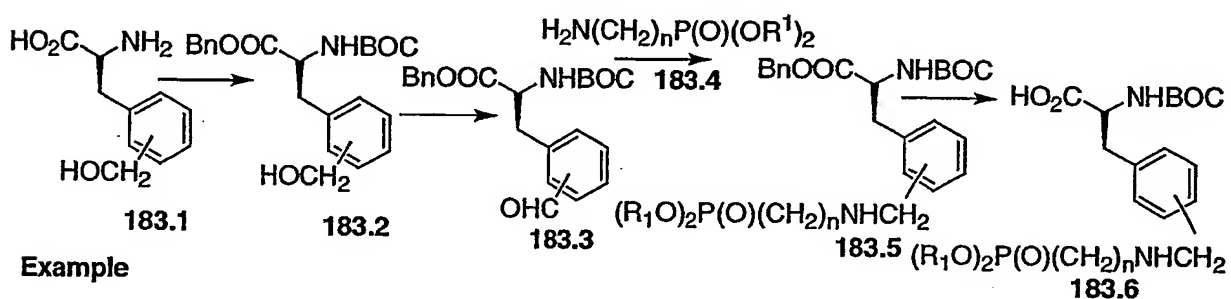


Example 3

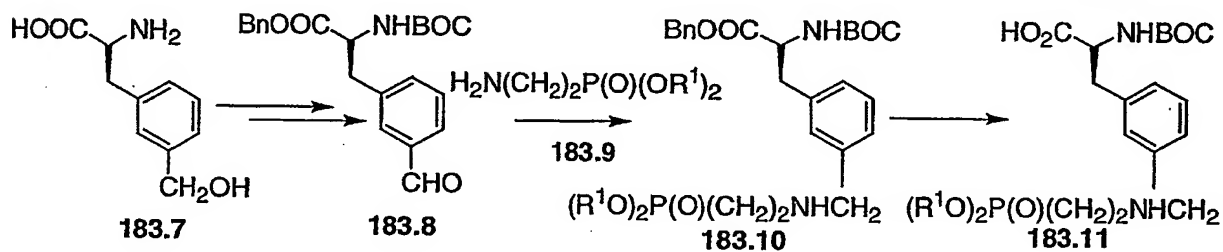


Scheme 183

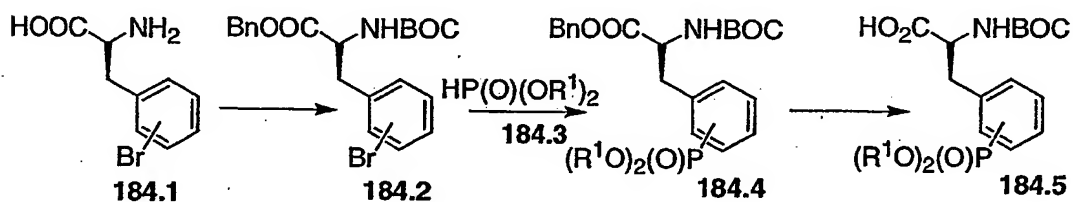
Method



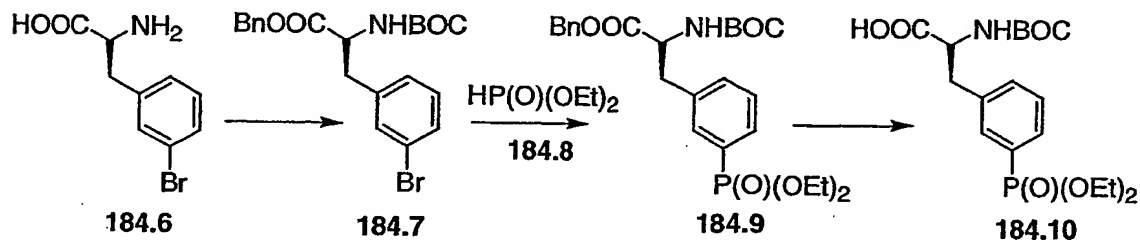
Example



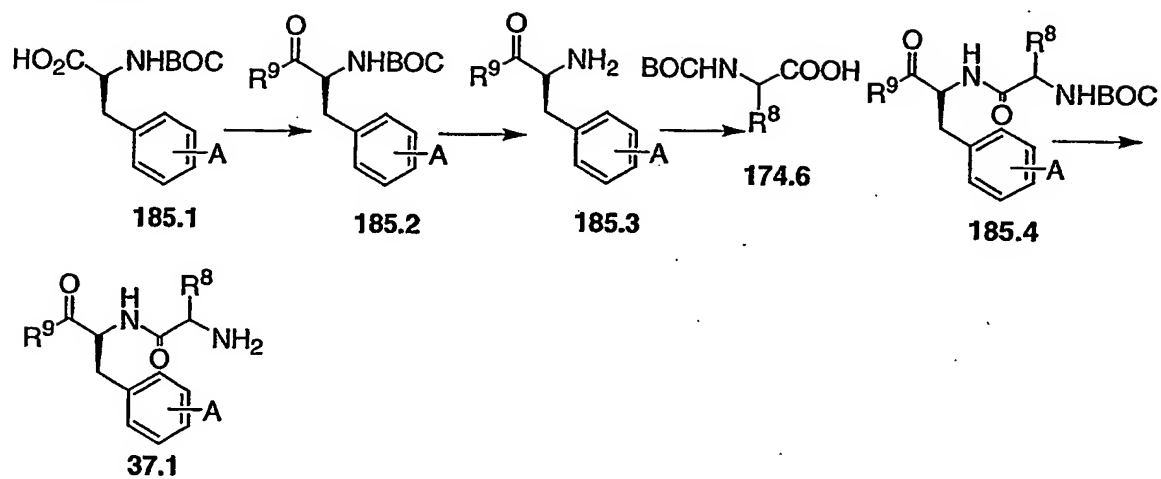
Scheme 184



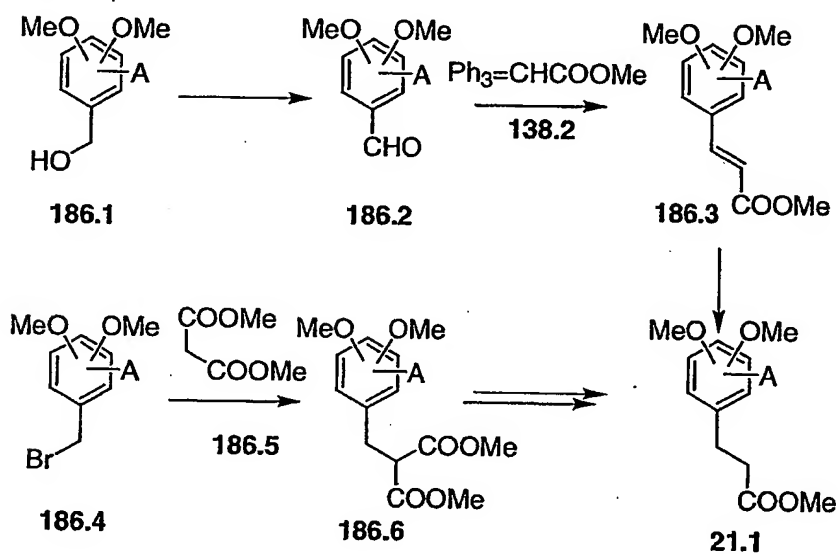
Example



Scheme 185

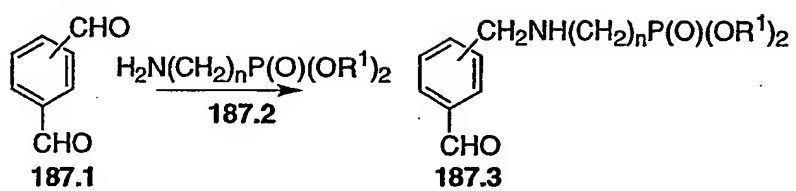


Scheme 186

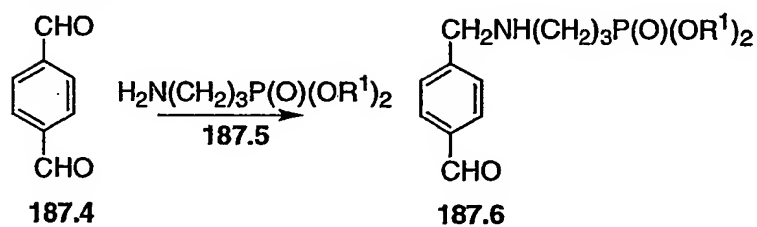


Scheme 187

Method

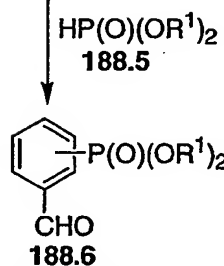
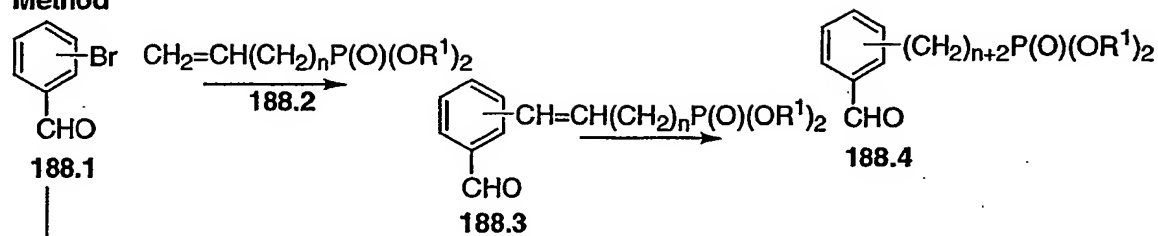


Example

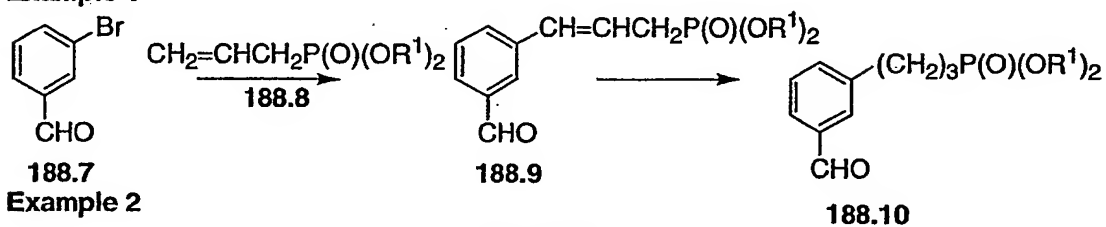


Scheme 188

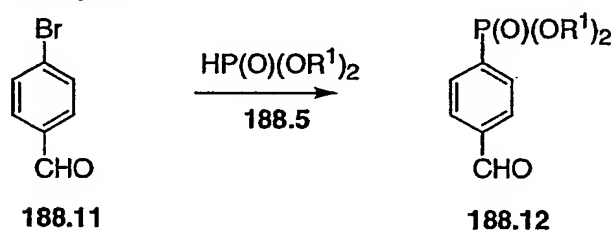
Method



Example 1

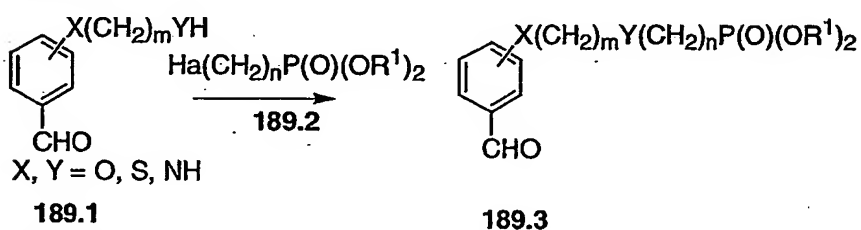


Example 2

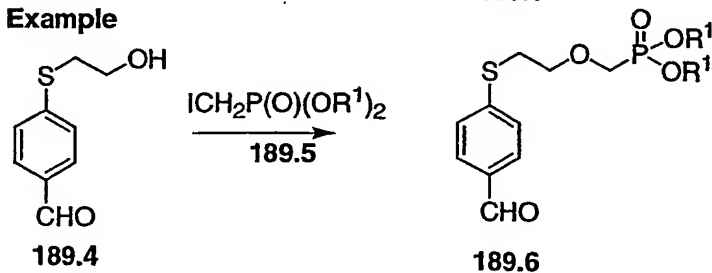


Scheme 189

Method

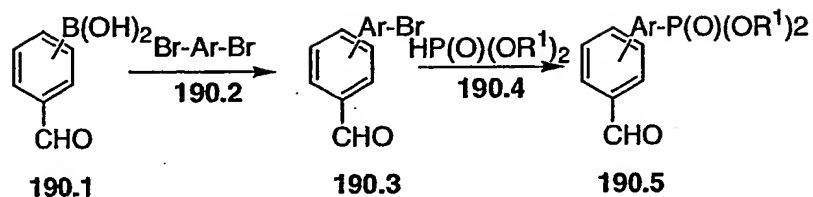


Example

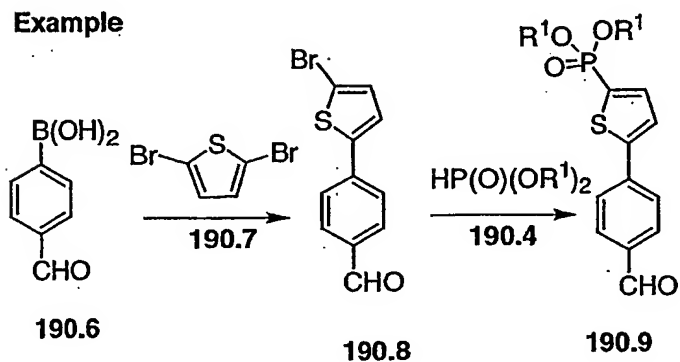


Scheme 190

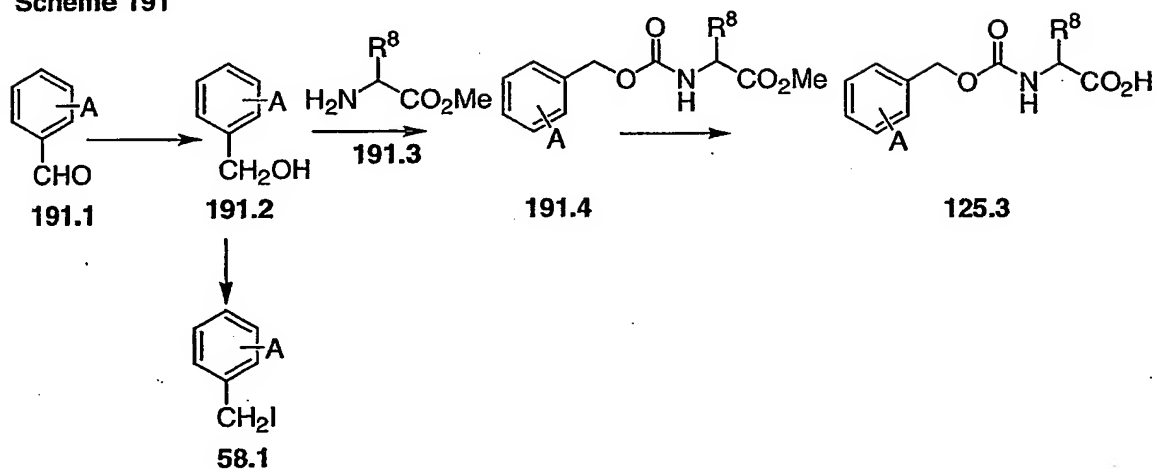
Method



Example



Scheme 191



5 Preparation of phosphonate-substituted decahydroquinolines 17.1.

Schemes 192 – 97 illustrate the preparation of decahydroisoquinoline derivatives 17.1 in which the substituent A is either the group link P(O)(OR¹)₂ or a precursor, such as [OH], [SH], Br.

The compounds are employed in the preparation of the intermediate phosphonate esters 5, 12 and 21.

Scheme 192 illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate 192.4 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 192.1, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 192.2. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 192.2, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 192.3. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 192.3 is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 192.4, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 192.4 is obtained from 2-hydroxyphenylalanine 192.5, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate 192.5 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 192.4, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline 192.6. The reduction is also performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline 192.4 is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°C, to afford the decahydroisoquinoline 192.6.

Protection of the carboxyl and NH groups present in **192.6**, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example,
5 pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **192.9**, in which R is trichloroethyl and R¹ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butoxy aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol
10 **192.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **192.10**.

The alcohol **192.6** is converted into the thiol **192.13** and the amine **192.14**, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry.

15 For example, the alcohol **192.6** is converted into an activated ester such as the trifluoromethanesulfonyloxy ester or the methanesulfonate ester **192.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **192.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement
20 of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **192.13**.

For example, the mesylate **192.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate **192.12**, in which R is COCH₃. The product then treated with a mild
25 base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **192.13**.

The mesylate **192.7** is treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, followed by deprotection as described previously, to afford the amine
30 **192.14**.

For example, the mesylate **192.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such

as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 192.8, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine 192.14.

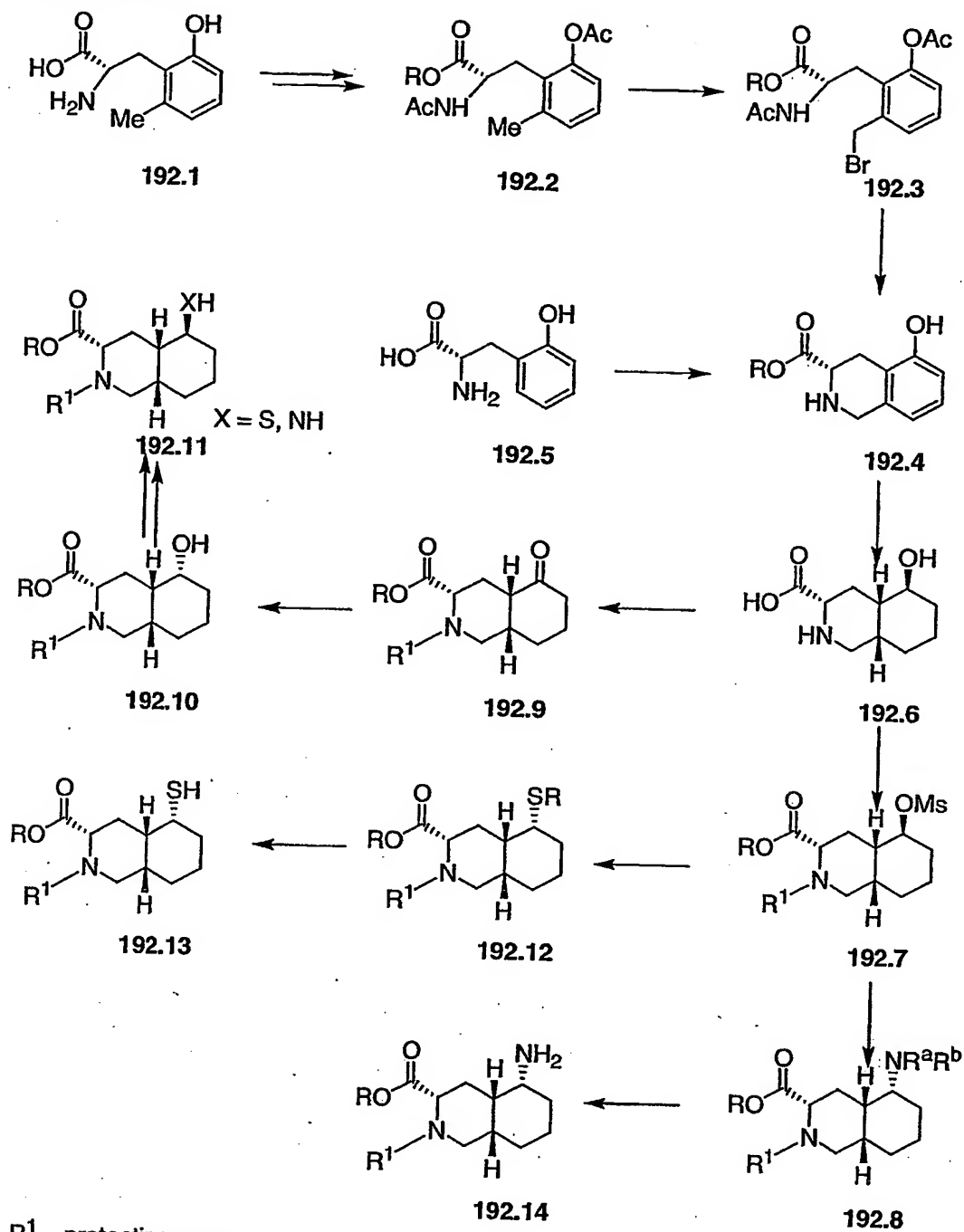
- 5 The application of the procedures described above for the conversion of the β -carbinol 192.6 to the α -thiol 192.13 and the α -amine 192.14 can also be applied to the α -carbinol 192.10, so as to afford the β -thiol and β -amine, 192.11.

- Scheme 193 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.
- 10 In this procedure, an alcohol, thiol or amine 193.1 is reacted with a bromoalkyl phosphonate 193.2, under the conditions described above for the preparation of the phosphonate 155.4 (Scheme 155), to afford the displacement product 193.3. Removal of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described
- 15 below, (Scheme 197) then yields the amine 193.4.

- For example, the thiol 193.5, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, 193.6, the preparation of which is described in J.
- 20 Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product 193.7. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme 197) then yields the amine 193.8.

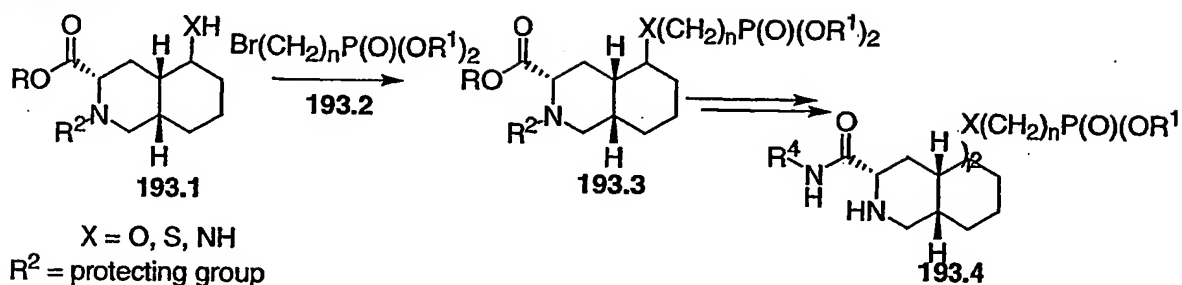
- Using the above procedures, but employing, in place of the α -thiol 193.5, the alcohols, thiols or amines 192.6, 192.10, 192.11, 192.13, 192.14, of either α - or β -orientation, there are
- 25 obtained the corresponding products 193.4, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 192

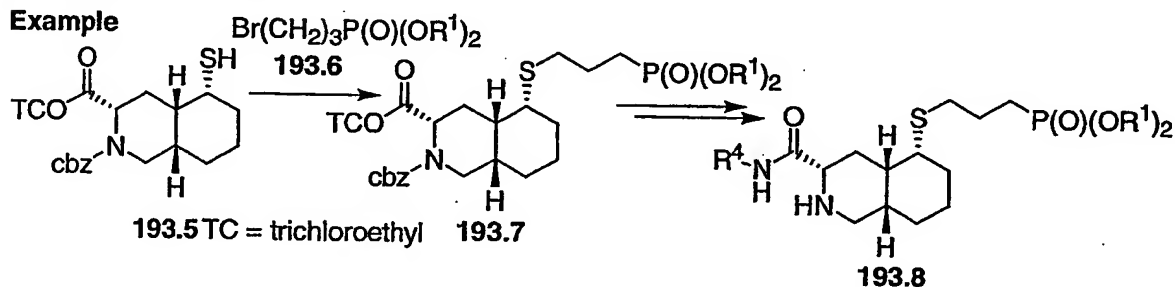


Scheme 193

Method

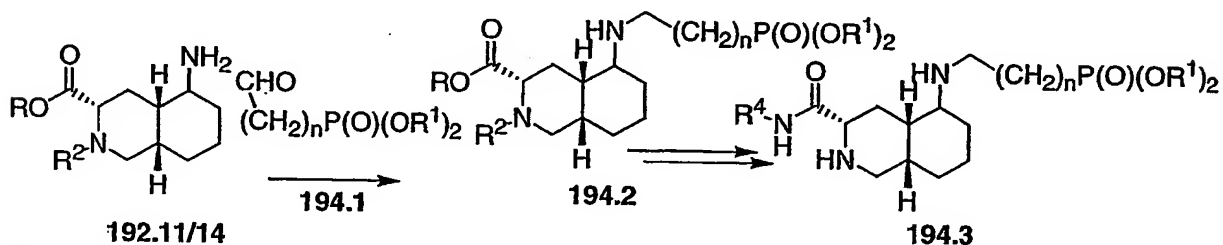


Example

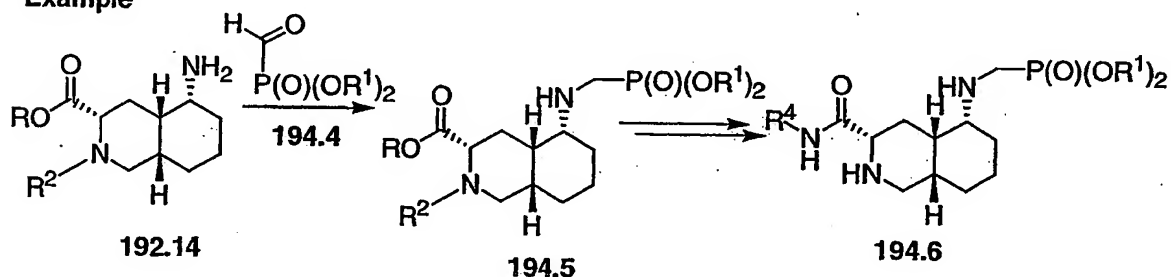


Scheme 194

Method



Example



Scheme 194 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **192.14** or **192.11** are reacted with a phosphonate aldehyde **194.1**, in the presence of a reducing agent, to afford the alkylated amine **194.2**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described below, (Scheme **197**) then yields the amine **194.3**.

- 5 For example, the protected amino compound **192.14** is reacted with a dialkyl formylphosphonate **194.4**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **194.5**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **194.6**.
- 10 Using the above procedures, but employing, instead of the α -amine **192.14**, the β isomer, **192.11** and/or different aldehydes **194.1**, there are obtained the corresponding products **194.3**, in which the orientation of the side chain is the same as that of the amine precursor.

- 15 Scheme **195** depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.
- In this procedure, a dialkyl mercaptoalkyl phosphonate **195.2** is reacted with a mesylate **195.1**, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product **195.3**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.4**.
- 20

- For example, the protected mesylate **195.5** is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate **195.6**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thioether phosphonate **195.7**. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described in Scheme **197**, then yields the amine **195.8**.
- 25

- Using the above procedures, but employing, instead of the phosphonate **195.6**, different phosphonates **195.2**, there are obtained the corresponding products **195.4**.
- 30

Scheme 196 illustrates the preparation of decahydroisoquinoline phosphonates 196.4 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 196.1 and a bromomethyl-substituted arylphosphonate 196.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 196.1. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate is employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is employed. The displacement reaction affords the ether, thioether or amine compounds 196.3. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.4.

For example, the alcohol 196.5 is reacted at ambient temperature with a dialkyl 3-bromomethyl benzylphosphonate 196.6, the preparation of which is described above, (Scheme 143). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate 196.6, to afford the product 196.7. Deprotection of the ester group, followed by conversion of the acid to the R⁴NH amide and N-deprotection, as described in Scheme 197, then yields the amine 196.8.

Using the above procedures, but employing, instead of the β -carbinol 196.5, different carbinols, thiols or amines 196.1, of either α - or β -orientation, and/or different phosphonates 196.2, in place of the phosphonate 196.6, there are obtained the corresponding products 196.4 in which the orientation of the side-chain is the same as that of the starting material 196.1.

Schemes 193 - 196 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 197 illustrates the conversion of the latter group of compounds 197.1 (in which the group A is link-P(O)(OR¹)₂ or optionally protected precursor substituents, such as, for example, OH, SH, or NH₂ to the corresponding R⁴NH amides 17.1.

As shown in Scheme 197, the ester compounds 197.1 are deprotected to form the corresponding carboxylic acids 197.2. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and

the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid 197.2 to the R⁴NH amide 197.4 is then accomplished by reaction, as described in Scheme 1, of the carboxylic acid, or an activated derivative thereof, with the amine R⁴NH₂ (197.3) to afford the amide 197.4. Deprotection of the NR² group, as described above, then affords the free amine 17.1.

Preparation of carbamates.

- 10 The phosphonate esters 13 - 20 in which the R¹⁰ is alkoxy, and the phosphonate esters 22 contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
- 15 Scheme 198 illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme 198, in the general reaction generating carbamates, a carbinol 198.1, is converted into the activated derivative 198.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 198.2 is then reacted with an amine 198.3, to afford the carbamate product 198.4. Examples 1 - 7 in
- 20 Scheme 198 depict methods by which the general reaction is effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.
- Scheme 198, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 198.1. In this procedure, the carbinol is reacted with phosgene, in an inert solvent such as toluene, at about 0°C, as described in Org. Syn. Coll. Vol. 3, 167, 1965,
- 25 or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 198.6. The latter compound is then reacted with the amine component 198.3, in the presence of an organic or inorganic base, to afford the carbamate 198.7. For example, the chloroformyl compound 198.6 is reacted with the amine 198.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of
- 30 aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 198.7. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 198, Example 2 depicts the reaction of the chloroformate compound 198.6 with imidazole to produce the imidazolide 198.8. The imidazolide product is then reacted with the amine 198.3 to yield the carbamate 198.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°C, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 198 Example 3, depicts the reaction of the chloroformate 198.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 198.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 198.19 - 198.24 shown in Scheme 198, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 198.19, N-hydroxysuccinimide 198.20, or pentachlorophenol, 198.21, the mixed carbonate 198.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 198.22 or 2-hydroxypyridine 198.23 is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 198 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 198.8 is employed. In this procedure, a carbinol 198.5 is reacted with an equimolar amount of carbonyl diimidazole 198.11 to prepare the intermediate 198.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 198.8 is then reacted with an equimolar amount of the amine RNH₂ to afford the carbamate 198.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 198.7.

Scheme 198, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole 198.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 198.12, to afford the alkoxycarbonyl product 198.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine RNH₂ to afford the

carbamate **198.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80°C as described in Syn., 1977, 704.

Scheme 198, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, **198.14**, is reacted with a carbinol **198.5** to afford the intermediate

5 alkyloxycarbonyl intermediate **198.15**. The latter reagent is then reacted with the amine RNH₂ to afford the carbamate **198.7**. The procedure in which the reagent **198.15** is derived from hydroxybenztriazole **198.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **198.15** is derived from N-hydroxysuccinimide **198.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **198.15** is derived from 2-hydroxypyridine
10 **198.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **198.15** is derived from 4-nitrophenol **198.24** is described in Syn. 1993, 199. The reaction between equimolar amounts of the carbinol ROH and the carbonate **198.14** is conducted in an inert organic solvent at ambient temperature.

Scheme 198, Example 7 illustrates the preparation of carbamates from alkoxy carbonyl azides
15 **198.16**. In this procedure, an alkyl chloroformate **198.6** is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide **198.16**. The latter compound is then reacted with an equimolar amount of the amine RNH₂ to afford the carbamate **198.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

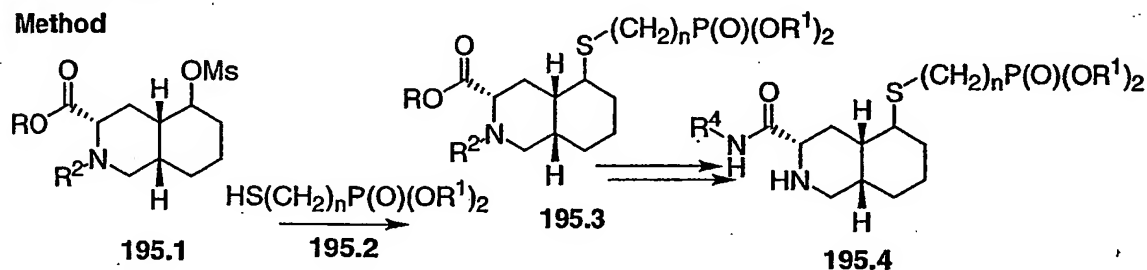
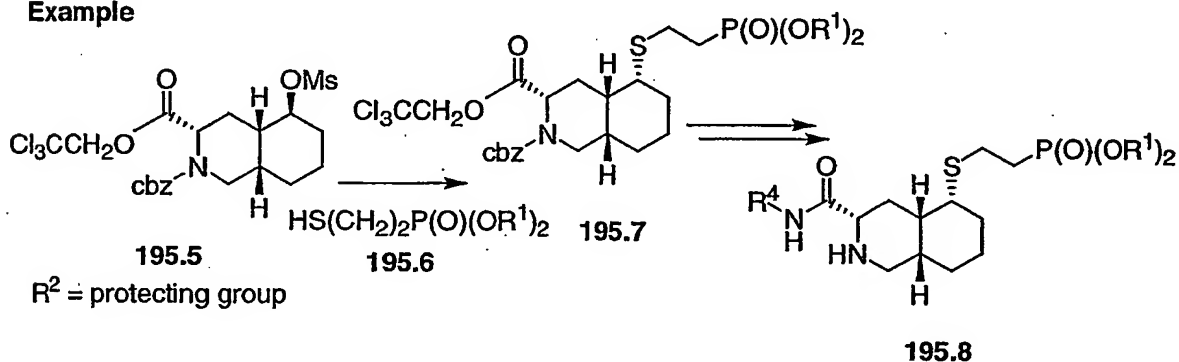
20 Scheme 198, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **198.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate
25 **198.7**.

Scheme 198, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **198.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane
30 and the like, to afford the carbamate **198.7**.

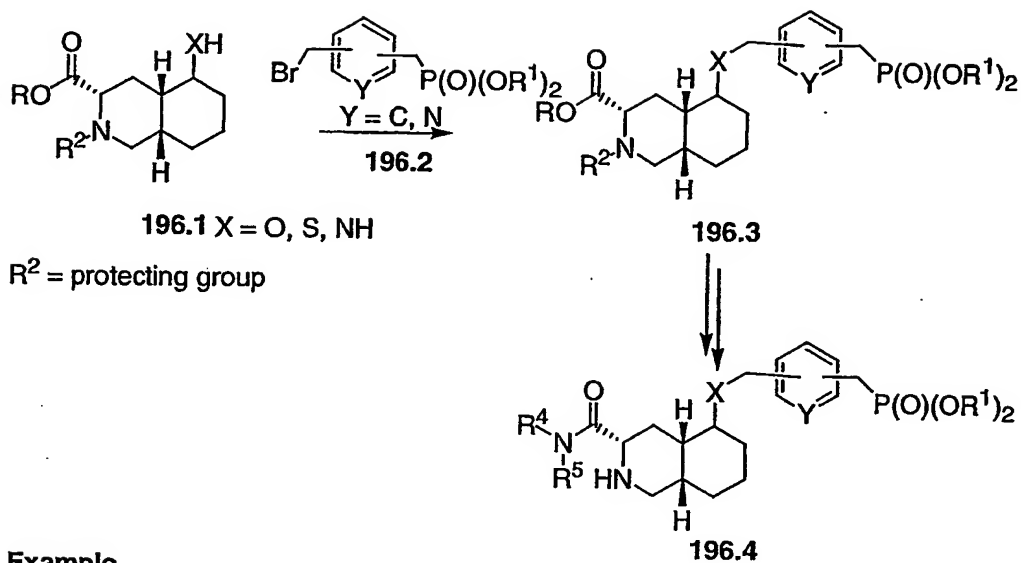
Scheme 198, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine RNH₂. In this procedure, which is described in Chem.

Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **198.7**.

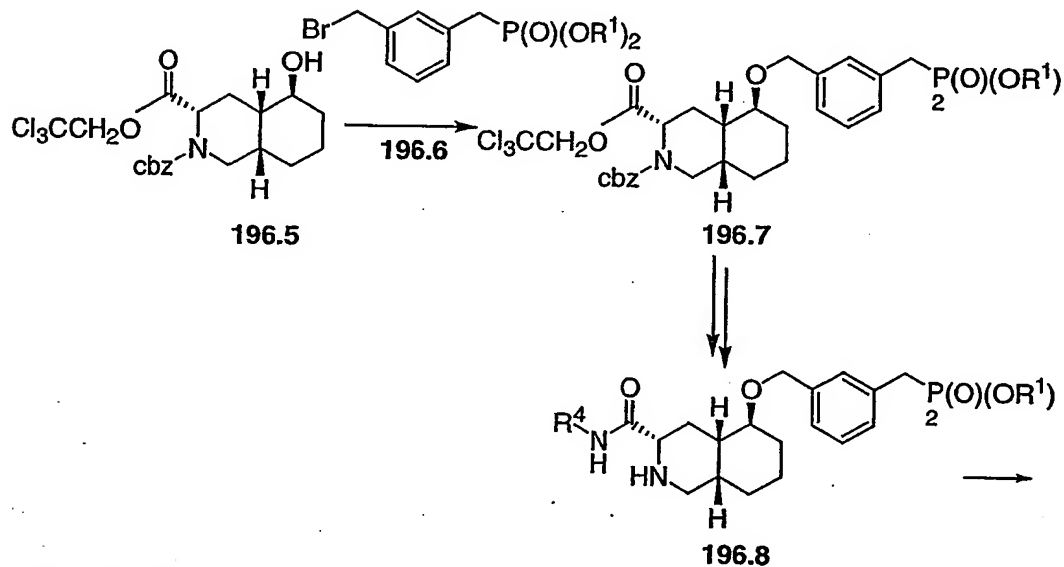
5

Scheme 195**Method****Example**

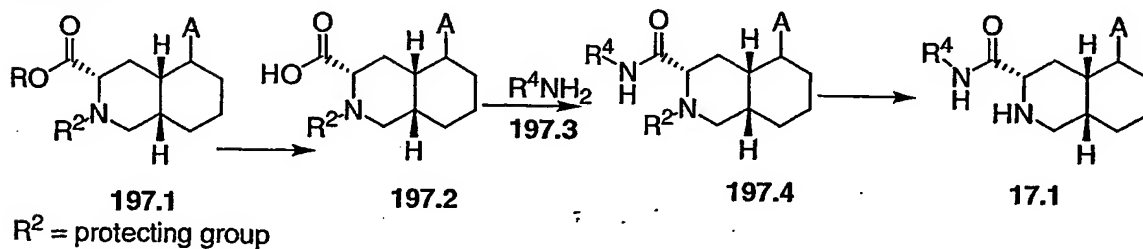
Scheme 196
Method



Example

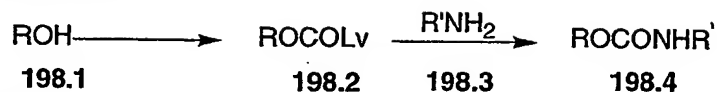


Scheme 197
Method

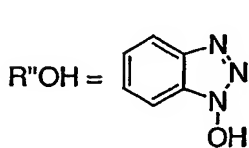
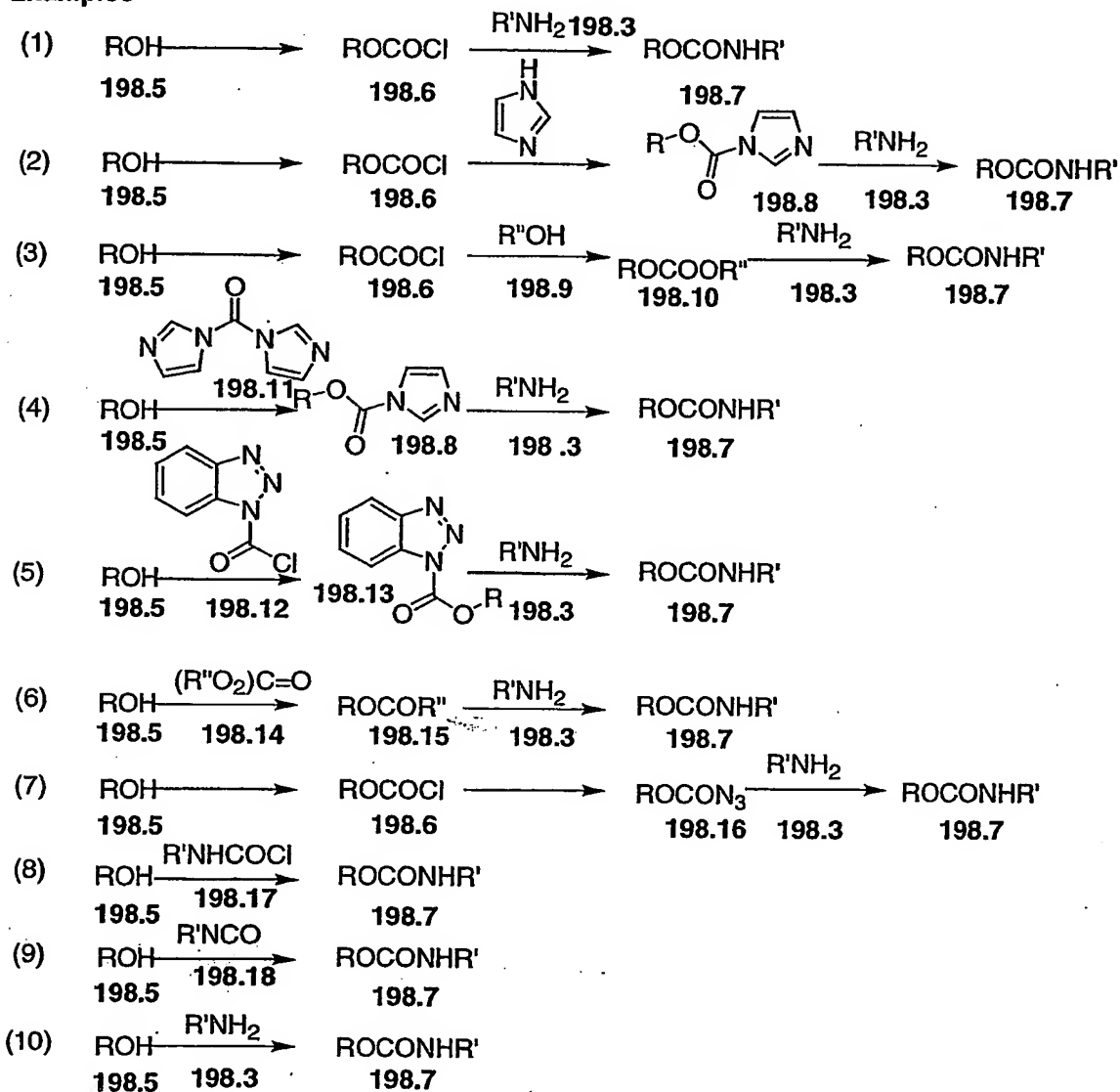


Scheme 198

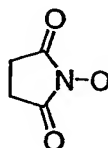
General reaction



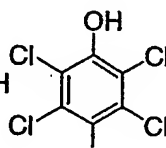
Examples



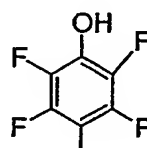
198.19



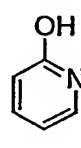
198.20



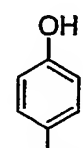
198.21



198.22



198.23



198.24

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 197 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to the phosphonate esters 1 - 24, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 199. The group R in Scheme 199 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1 - 24 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1 - 24. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 199.1 into the corresponding phosphonate monoester 199.2 (Scheme 199, Reaction 1) is accomplished by a number of methods. For example, the ester 199.1 in which R¹ is an aralkyl group such as benzyl, is converted into the monoester compound 199.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°C. The conversion of the diester 199.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 199.2 is effected by treatment of the ester 199.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 199.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters 199.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, are converted into the monoester 199.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **199.1** or a phosphonate monoester **199.2** into the corresponding phosphonic acid **199.3** (Scheme **199**, Reactions **2** and **3**) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **199.2** in which R¹ is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **199.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **199.2** in which R¹ is alkenyl such as, for example, allyl, is converted into the phosphonic acid **199.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **199.1** in which R¹ is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

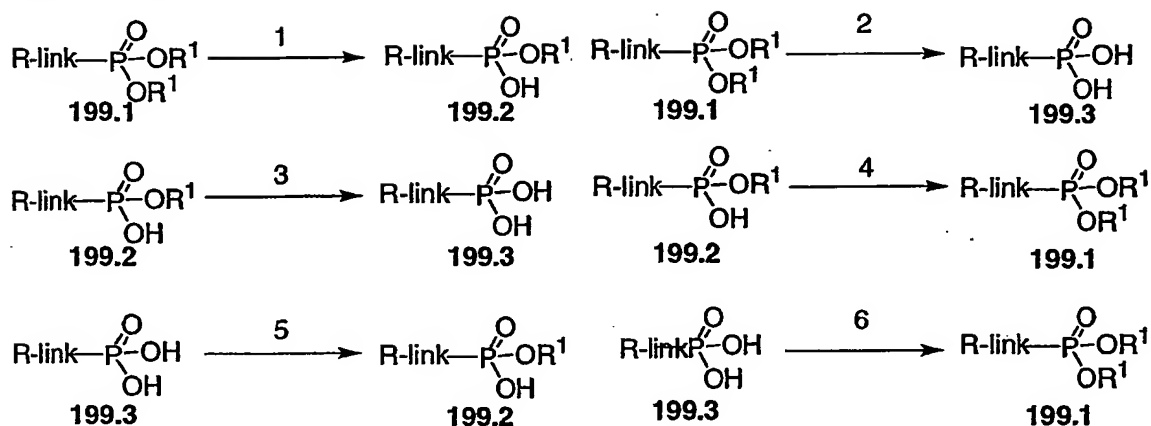
The conversion of a phosphonate monoester **199.2** into a phosphonate diester **199.1** (Scheme **199**, Reaction **4**) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **199.2** is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **199.2** to the diester **199.1** is effected by the use of the Mitsunobu reaction, as described above (Scheme **142**). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **199.2** is transformed into the phosphonate diester **199.1**, in which the

introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **199.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **199.1**.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **199**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ **199.3** is transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **199.1** (Scheme **199**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca $70^\circ C$. Alternatively, phosphonic acids **199.3** are transformed into phosphonic esters **199.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **199.1**.

Scheme 199



General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes 133 - 192) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into indanols (Schemes 133 - 137) are applicable to the introduction of phosphonate moieties into phenylpropionic acids, thiophenols, tert. butylamines, pyridines, benzyl halides, ethanolamines, aminochromans, phenylalanines and benzyl alcohols, and the methods described for the introduction of phosphonate moieties into the above-named substrates (Schemes 138 - 192) are applicable to the introduction of phosphonate moieties into indanol substrates.

Preparation of phosphonate intermediates 23 and 24 with phosphonate moieties incorporated into the R², R³, R⁵, R¹⁰ or R¹¹ groups.

The chemical transformations described in Schemes 1 - 192 illustrate the preparation of compounds 1 - 22 in which the phosphonate ester moiety is attached to the indanol moiety, (Schemes 1 - 4, 76 - 84), the phenyl group (Schemes 5 - 8, 21 - 24, 37 - 40, 49 - 52, 58 - 61, 67 - 68, 74, 75, 101 - 108, 125 - 132) the tert. butylamine group, (Schemes 9 - 12, 25 - 28, 41 - 44, 109 - 116), the pyridine group (Schemes 13 - 16), the decahydroisoquinoline group (Schemes 17 - 20, 45 - 48, 117 - 124), the ethanolamine group (Schemes 29 - 32, 93 - 100), the aminochroman group (Schemes 33 - 36, 85 - 92), and the thiophenyl group

(Schemes 53 – 57, 62 – 66, 69 – 73). The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$. The resultant phosphonate-containing analogs, designated as $R^{2a}R^{3a}NH$, $R^{5a}SH$, $R^{5a}CH_2I$, $R^{10a}CO$, $R^{11a}SH$, and $R^{11a}CH_2CH(NH_2)COOH$ are then, using the procedures described above, employed in the preparation of the compounds 23 and 24. The procedures required for the utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2R^3NH , R^5SH , R^5CH_2I , $R^{10}CO$, $R^{11}SH$, and $R^{11}CH_2CH(NH_2)COOH$.

For example, Schemes 200-204 and Schemes 205-207 depict the introduction of the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, $[OH]$, $[NH_2]$, $[SH]$ onto the R^2R^3NH amines A10a and A10b in Chart 4, to give amines 200.5 and 205.10 respectively. These amine products are then utilized in the generation of compounds 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ in Chart 3 following the same procedures outlined in Schemes 13 and 15 but replacing the amine 13.1 with 200.5 or 205.10 respectively.

Preparation of piperazine furan compounds 200.5 with phosphonate attachments

Schemes 200 - 204 depict the preparation of the piperazine furan aryl phosphonate compounds 200.5 that are employed in the preparation of the phosphonate esters 23 where R^2R^3NH is now $R^{2a}R^{3a}NH$ as described above.

Scheme 200 depicts the preparation of piperazine biaryl phosphonates in which the terminal aryl ring bears the phosphonate moiety through a linking group. Methods for the preparation of the reagents 200.2 are shown in Schemes 201-204. Furan 200.1 prepared as described in WO02/096359, is treated with the aryl bromide 200.2 in the presence of palladium catalyst by the method of Gronowitz et al. (J. Heterocyclic Chemistry, 1995, 35, p. 771) to give 200.3. The product 200.3 is then subjected to the sequence of reactions and conditions described in WO02/096359 to prepare the piperazine 200.5. The preparation of reagent 200.6 where $R^4 = CH_2CF_3$ is also described in WO02/096359. Alternatively, deprotection of amines 164.1 by treatment with trifluoroacetic acid at room temperature as described in Int. J. Pept. Protein Res., 12, 258, 1978, followed by treatment with alloc chloro formate and a base such as

pyridine, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 526-527 yields **200.6** where R^4 is as defined in Chart 1.

Scheme **201** depicts the preparation of phosphonates **200.2** in which the phosphonate moiety is attached to the phenyl ring by means of a heteroatom and an alkyl chain. Many halogenated aromatic compounds are commercially available or can be generated from readily available aromatic compounds through aromatic substitution. Methods for chlorinating or brominating an aryl ring can be found in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999 p619. The phenol, thiol or amine **201.1** is reacted with a derivative of a hydroxymethyl dialkylphosphonate **140.2**, in which Lv is a leaving group such as methanesulfonyloxy and the like. The reaction is conducted in a polar aprotic solvent, in the presence of an organic or inorganic base, to afford the displacement product **201.2**. For example, the phenols **201.5** (Aldrich) or **201.9** (Apollo-Chem) are reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **140.6**, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether products. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°C, to afford the products **201.6** and **201.10** respectively. Alternatively treatment of amine **201.11** (Apollo) or **201.7** (Aldrich) with the dialkyl trifluoromethylsulfonyloxymethyl phosphonate **140.6** in the presence of a base as described above affords **201.12** and **201.8** respectively.

Using the above procedures, but employing, in place of the phenols and amines, different phenols, thiols or amines **201.1**, and /or different dialkyl trifluoromethyl-sulfonyloxymethyl phosphonates **140.2**, the corresponding products **201.2** are obtained.

Scheme **202** illustrates the preparation of compounds in which the phosphonate group is attached by means of an aminoalkyl chain. In this procedure, the aldehyde **202.1** is reacted, under reductive amination conditions, as described in Scheme 135, with a dialkyl aminoalkyl phosphonate **202.2**, to give the amine **202.3**.

For example, the aldehyde **202.4** (Aldrich) is reacted in ethanol with a dialkyl aminoethyl phosphonate **166.5**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and sodium triacetoxyborohydride, to produce the amine **202.5**.

Using the above procedures, but employing, in place of the aldehyde, 202.4 different aldehydes 202.1 and different phosphonates 202.2, the corresponding products 202.3 are obtained.

- 5 Scheme 203 illustrates the preparation of aryl halides incorporating phosphonate groups attached by means of an amide group. In this procedure, a carboxy-substituted aryl halide 203.1 is coupled, as described in Scheme 1, with a dialkyl aminoalkyl phosphonate 202.2 to prepare the amide 203.2.

For example, 2-chloro-4-bromobenzoic acid 203.4, the preparation of which is described in
10 Bioorg. Med. Chem. Lett. 2001, 11, 10, p. 1257, is coupled in dimethylformamide solution, in the presence of dicyclohexylcarbodiimide, with a dialkyl aminoethyl phosphonate 166.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676, to afford the amide 203.5. Using the above procedures, but employing, in place of the benzoic acid 203.4, different benzoic acids 203.1, and/or different aminoalkyl phosphonates 202.2, the corresponding
15 products 203.2 are obtained.

Scheme 204 illustrates the preparation of phosphonate-substituted aryl halides in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a benzoic acid 203.1 is first methylated to give methyl ester 204.1 and then reduced with a reducing
20 agent, as described in J. Org. Chem. 1987, 52, p. 5419 to give alcohol 204.2. The alcohol 204.2 is then reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide 204.3. The bromide 204.3 is reacted with a sodium dialkyl phosphite 204.5 or a trialkyl phosphite, to give the product 204.4. For example, acid 204.6 (Lancaster) is converted to the methyl ester 204.7 by refluxing in
25 methanol and concentrated sulfuric acid and then reduced with lithium aluminum hydride in THF to give 204.8 as described above. The product 204.8 is reacted with hexabromoethane in the presence of triphenyl phosphine as described in Syn. 1983, p. 139 to give the bromide 204.9. This material is reacted with a sodium dialkyl phosphite 204.5, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 204.10. Alternatively, the bromomethyl
30 compound 204.9 is converted into the phosphonate 204.10 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure,

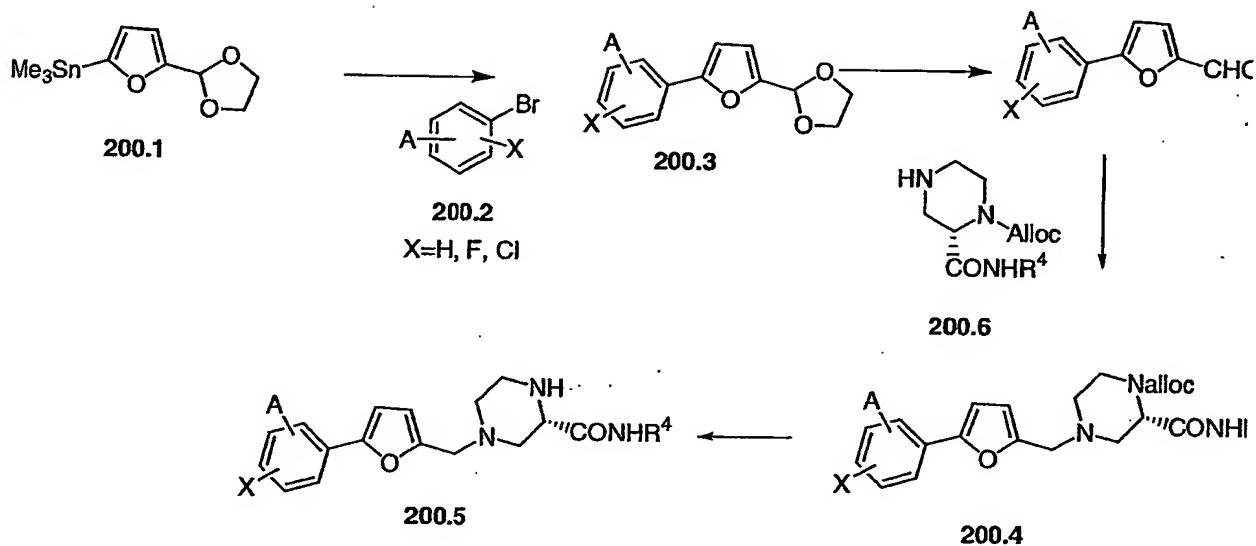
the bromomethyl compound **204.9** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100°C to produce the phosphonate **204.10**.

Using the above procedures, but employing, in place of the acid **204.6**, different acids **203.1**, and different phosphites **204.5** there are obtained the corresponding aryl halides **204.4**.

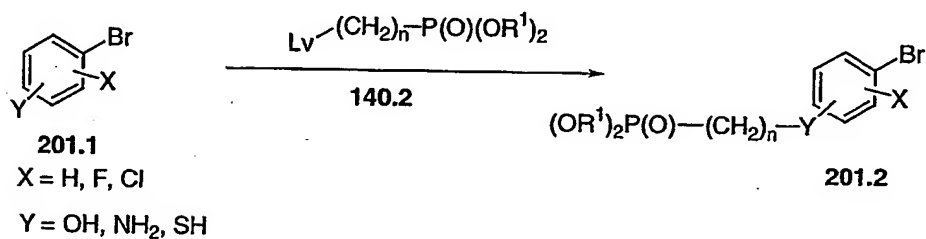
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The phosphonate-containing bromobenzene derivatives prepared as described in Schemes **201** - **204** are then transformed, as described in Scheme **200**, into the phenylfuran piperazine derivatives **200.5**.

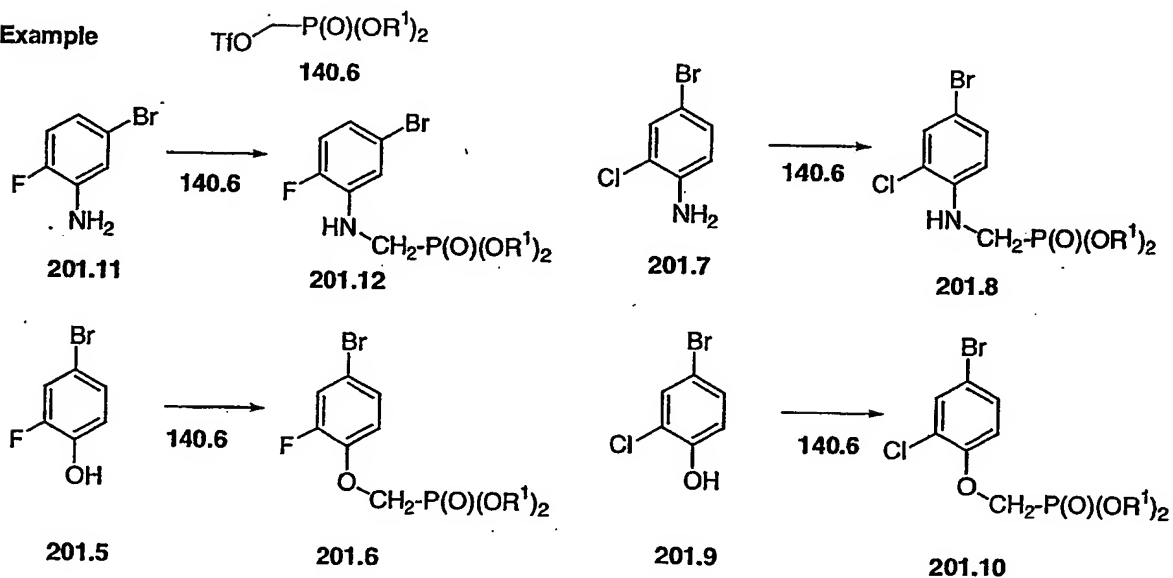
Scheme 200



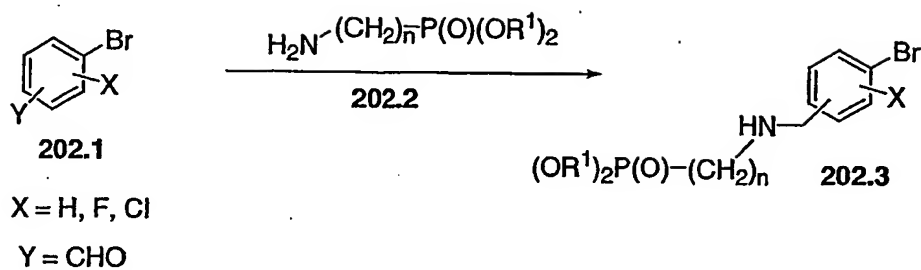
Scheme 201



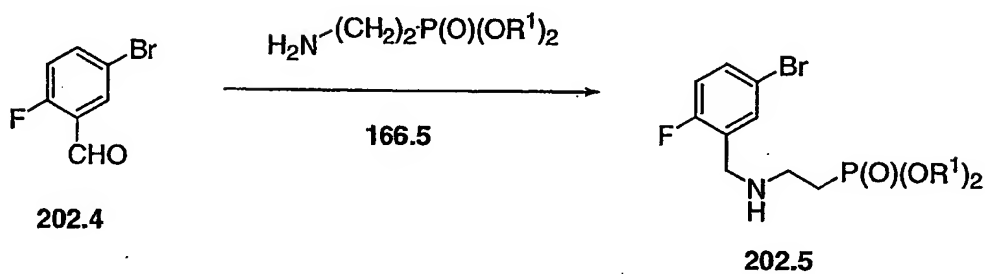
Example



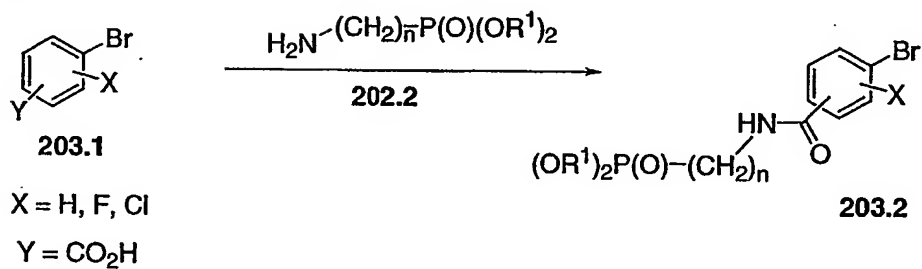
Scheme 202



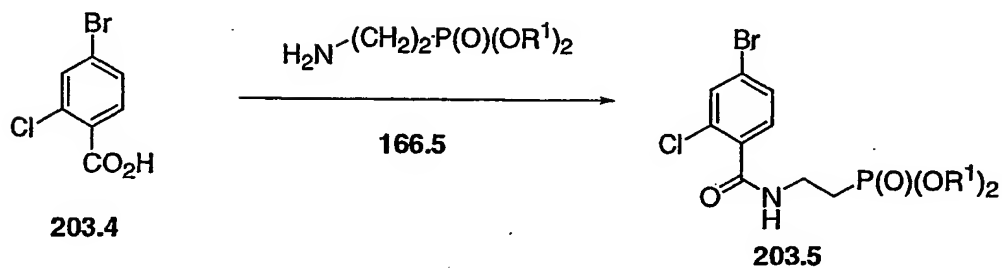
Example

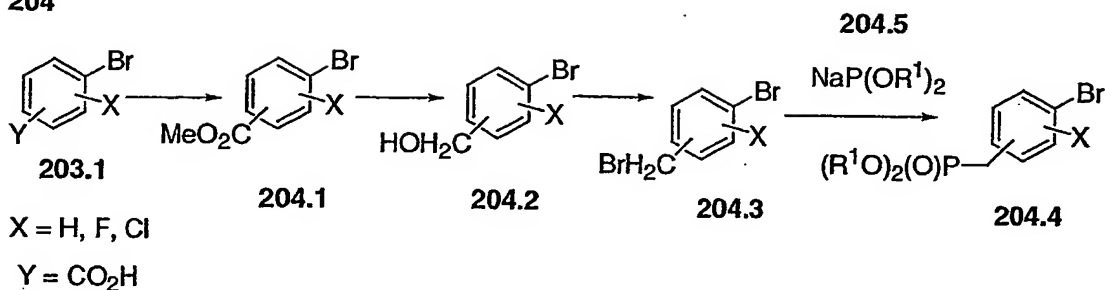


Scheme 203

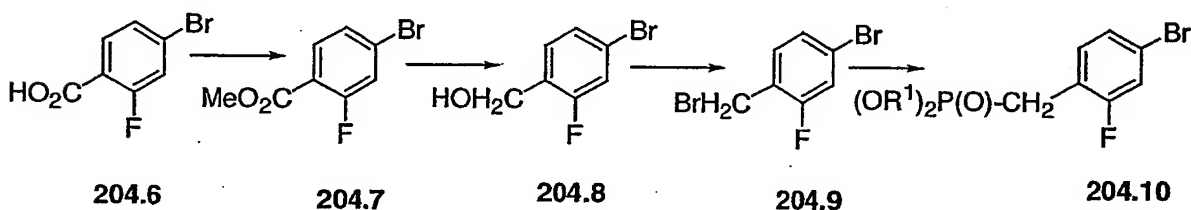


Example



Scheme
204

Example



Preparation of piperazine oxazole compounds 205.10 bearing phosphonate attachments

- 5 Schemes 205 - 207 depict the preparation of the piperazine oxazole phosphonate compounds 205.10 that are employed in the preparation of the phosphonate esters 23 where R²R³NH is now R^{2a}R^{3a}NH as described above.

- 10 Scheme 205 depicts the preparation of piperazine oxazole phosphonates 205.10 in which the terminal aryl ring bears the phosphonate moiety. The acid 205.1 is converted to the Weinreb amide, for example, as described in J. Med. Chem., 1994, 37, 2918, and then reacted with a methyl Grignard reagent e.g. MeMgBr. Examples of this procedure are reviewed in Org prep Proc Intl 1993, 25, 15. Ketone 205.3 is then brominated using conditions described in Comprehensive Organic Transformations, by R. C. Larock, 2nd Edition, 1999, p. 710-711.
- 15 For example, treatment of 205.3 with bromine in acetic acid yields 205.4. Conversion of the bromomethyl compound 205.4 into the piperazine derivative 205.10, via the intermediates 205.5 - 205.9, is effected by means of the reactions and procedures described in WO02/096359 for related compounds in which R⁴ is CH₂CF₃ and A is H.

Scheme 206 illustrates the preparation of benzoic acid phosphonates in which the phosphonate moiety is attached by means of alkylene chains and a heteroatom O, S or N. In this procedure, a benzoic acid 206.1 is protected with a suitable protecting group (see Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch5 and then
5 reacted with a an equimolar amount of a dialkyl phosphonate 206.3, in which Ha is a leaving group e.g. halogen, to afford the alkyl phosphonate product 206.4. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 206.2. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is
10 employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed. Following this reaction the product 206.4 is hydrolyzed by treatment with base to give the acid 206.5

For example, benzoic acid 206.6, (Aldrich) is reacted with diazomethane in ether at 0°C to give the methyl ester 206.7 or simply refluxed in acidic methanol. The ester in acetonitrile at
15 60°C is treated with one molar equivalent of a dialkyl iodomethyl phosphonate 206.8, (Lancaster) to give the ether product 206.9. This product 206.9 is then hydrolyzed by treatment with lithium hydroxide in aqueous THF to give the acid 206.10.

Using the above procedures, but employing, in place of the benzoic acid 206.6, different acids 206.1, and/or different haloalkyl phosphonates 206.3, the corresponding products 206.5 are
20 obtained.

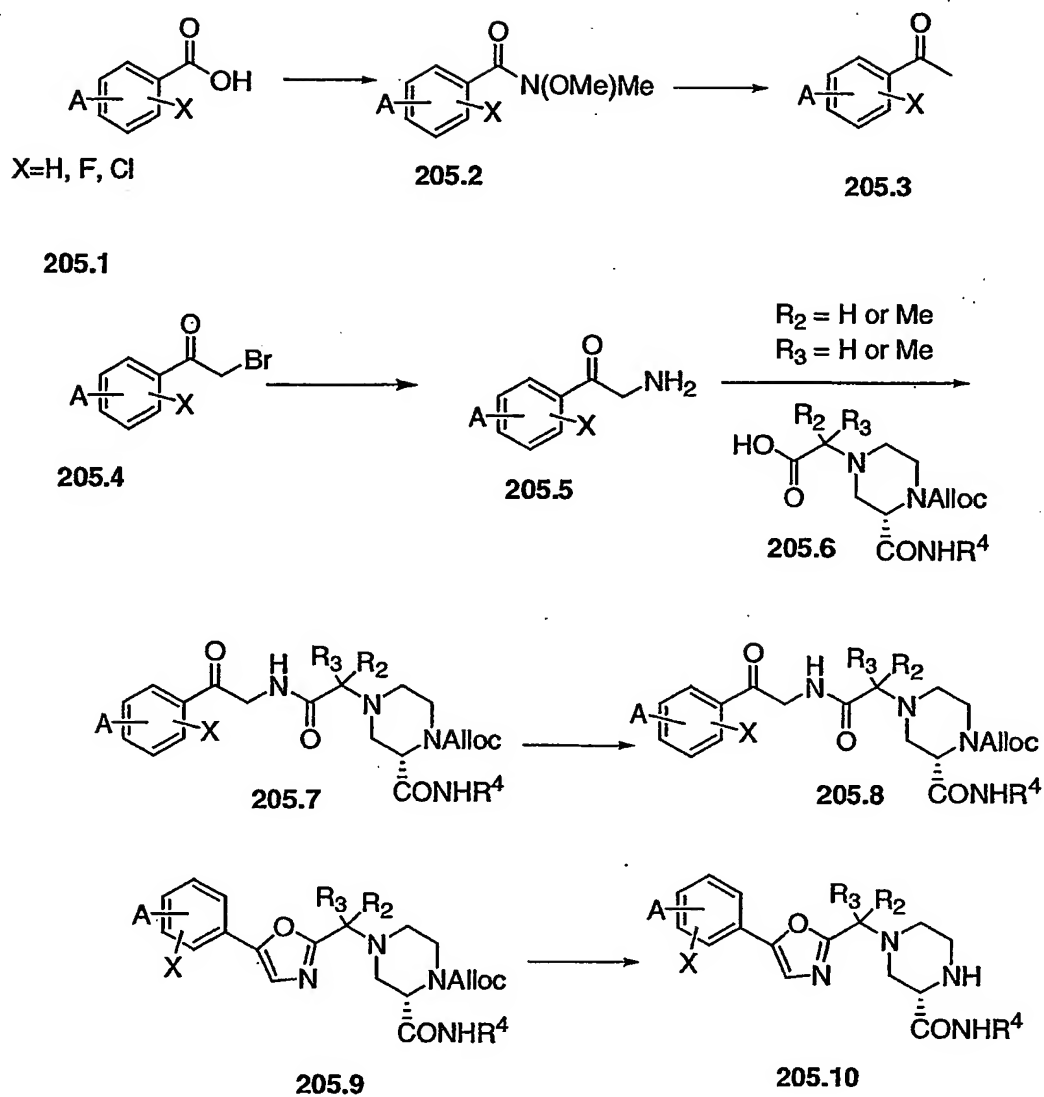
Scheme 207 depicts the preparation of phosphonate esters linked to a benzoic acid nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 207.3 is
25 coupled with an aromatic bromo compound 207.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
30 tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 207.4. Deprotection, or hydrogenation of the double bond

followed by deprotection, affords respectively the unsaturated phosphonate acid **207.5**, or the saturated analog **207.6** respectively.

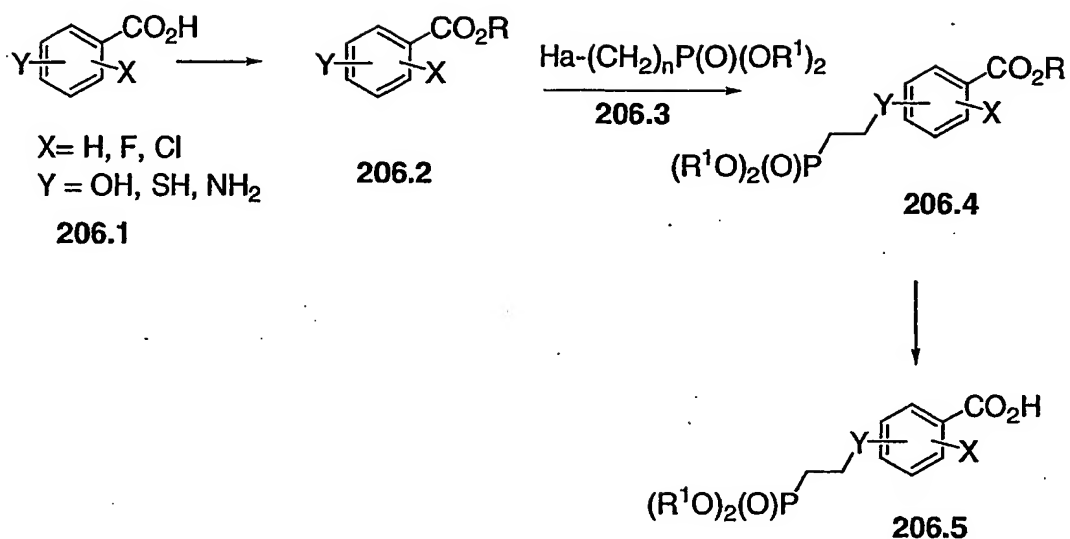
- For example, 4-bromo-3-fluorobenzoic acid **207.7** (Apollo) is converted to the tert butyl ester **207.8** by treatment with t-butanol and DCC in the presence of dimethylaminopyridine. The ester **207.8** is then reacted with a dialkyl 1-propenyl phosphonate **150.8**, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100°C to afford the coupled product **207.10**. Deprotection as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 406-408, then affords the acid **207.11**. Optionally, the acid **207.11** is subjected to catalytic or chemical reduction, for example using diimide, as described in Scheme 138, to yield the saturated product **207.12**.
- Using the above procedures, but employing, in place of the acid compound **207.7**, different acid compounds **207.1**, and/or different phosphonates **207.3**, there are obtained the corresponding products **207.5** and **207.6**.

- The phosphonate-containing benzoic acids, prepared as described in Schemes **206** and **207**, are then transformed, using the procedures shown in Scheme **205**, into the phenyloxazole piperazine derivatives **205.10**.

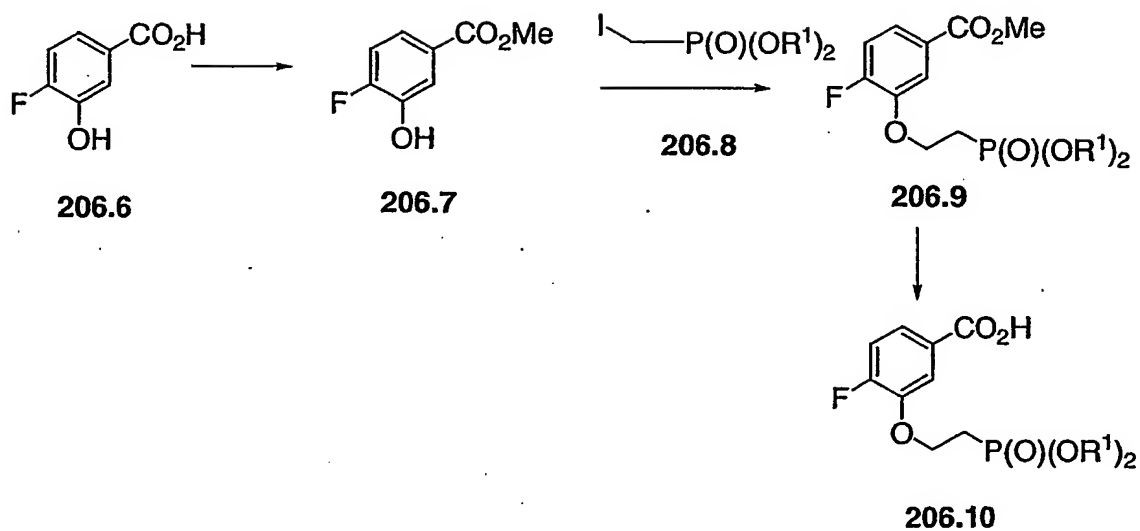
Scheme 205



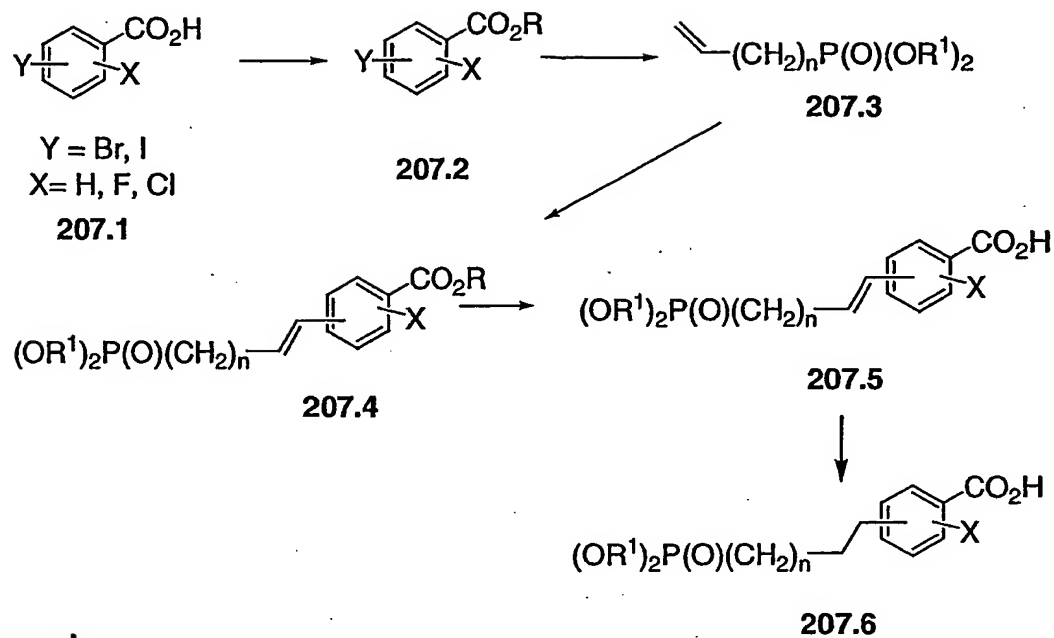
Scheme 206



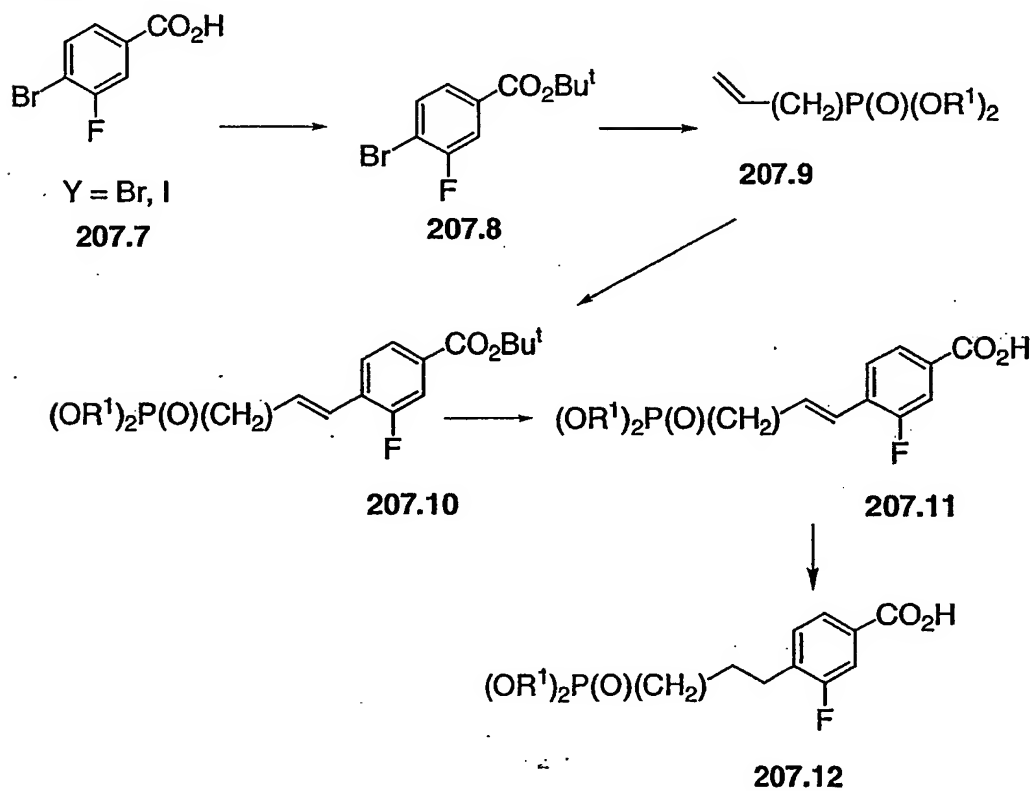
Example



Scheme 207



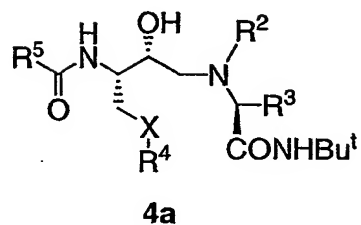
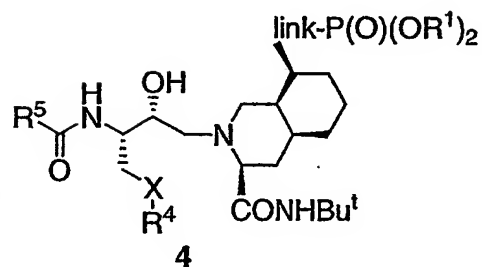
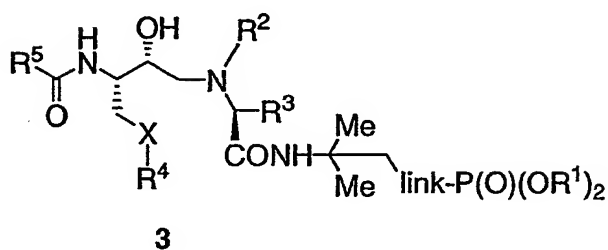
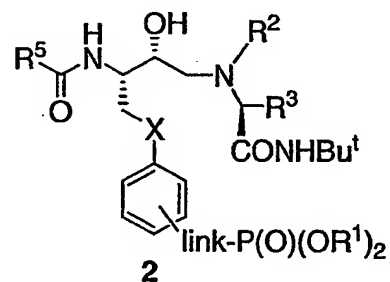
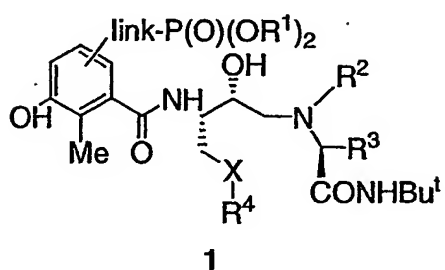
Example



Nelfinavir-like phosphonate protease inhibitors - (NLPPi)

Preparation of the intermediate phosphonate esters.

- 5 The intermediate phosphonate esters **1** to **4a** of this invention are shown in Chart 1. Subsequent chemical modifications, as described herein, permit the synthesis of the final compounds of this invention.
- The structures of the amine components $R^2NHCH(R^3)CONHBu^t$ **6-20e** are shown in Chart 2. Although specific stereoisomers of some of the amines are shown, all stereoisomers of the
- 10 amine components are utilized. Chart 2 also illustrates that, in addition to the tert. butyl amines **5**, the corresponding 2,2,2-trifluoroethyl and 2-methylbenzyl amides are utilized in the synthesis of the phosphonate intermediate compounds of this invention.
- Chart 3 depicts the structures of the R^4 components **21-26**. Charts **4a-4c** illustrate the structures of the carboxylic acid components R^5COOH , **C1-C49**.
- 15 The intermediate compounds **1** to **4a** incorporate a phosphonate moiety connected to the a nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts **5** and **5a** illustrate examples of the linking groups **38-59** present in the structures **1-4a**, and in which "etc" refers to the scaffold, e.g., nelfinavir.
- Schemes **1 - 50** illustrate the syntheses of the intermediate phosphonate compounds of this
- 20 invention, **1-4a**, and of the intermediate compounds necessary for their synthesis.

Chart 1. Structures of phosphonate ester intermediate compounds

$R^1 = \text{H, alkyl, alkenyl, aryl, aralkyl}$

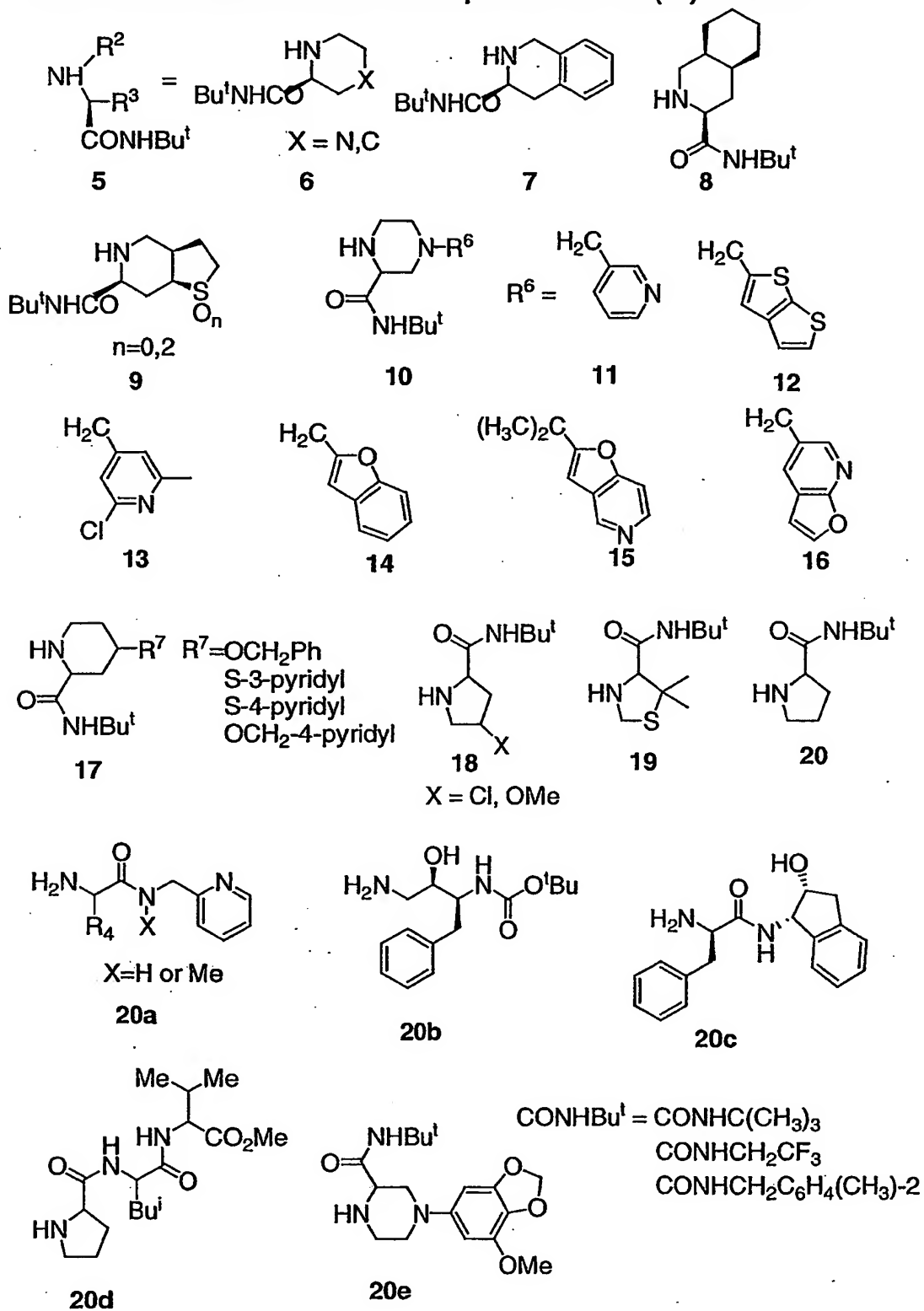
Chart 2. Structures of the amine component $R^2NHCH(R^3)CONHBu^t$ 

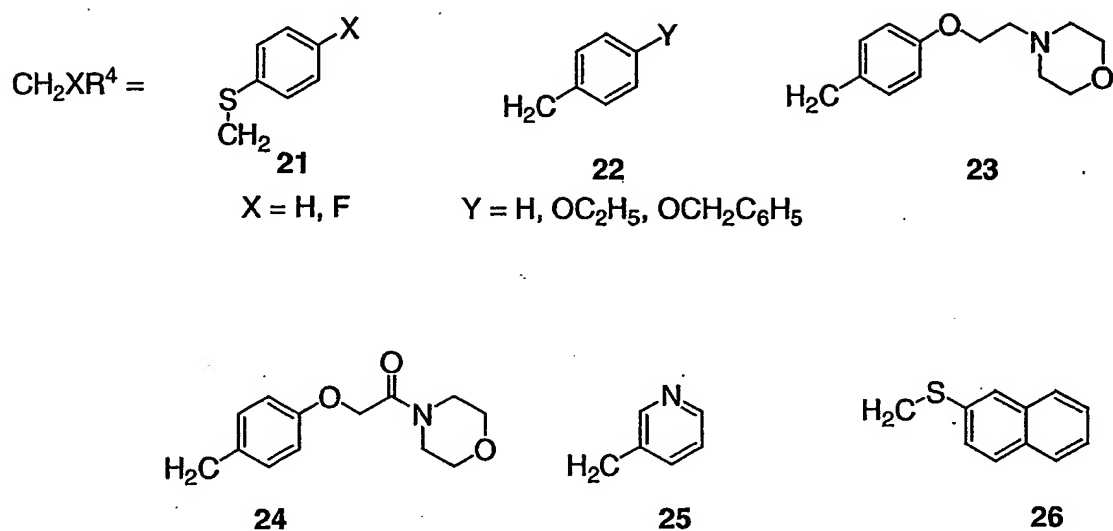
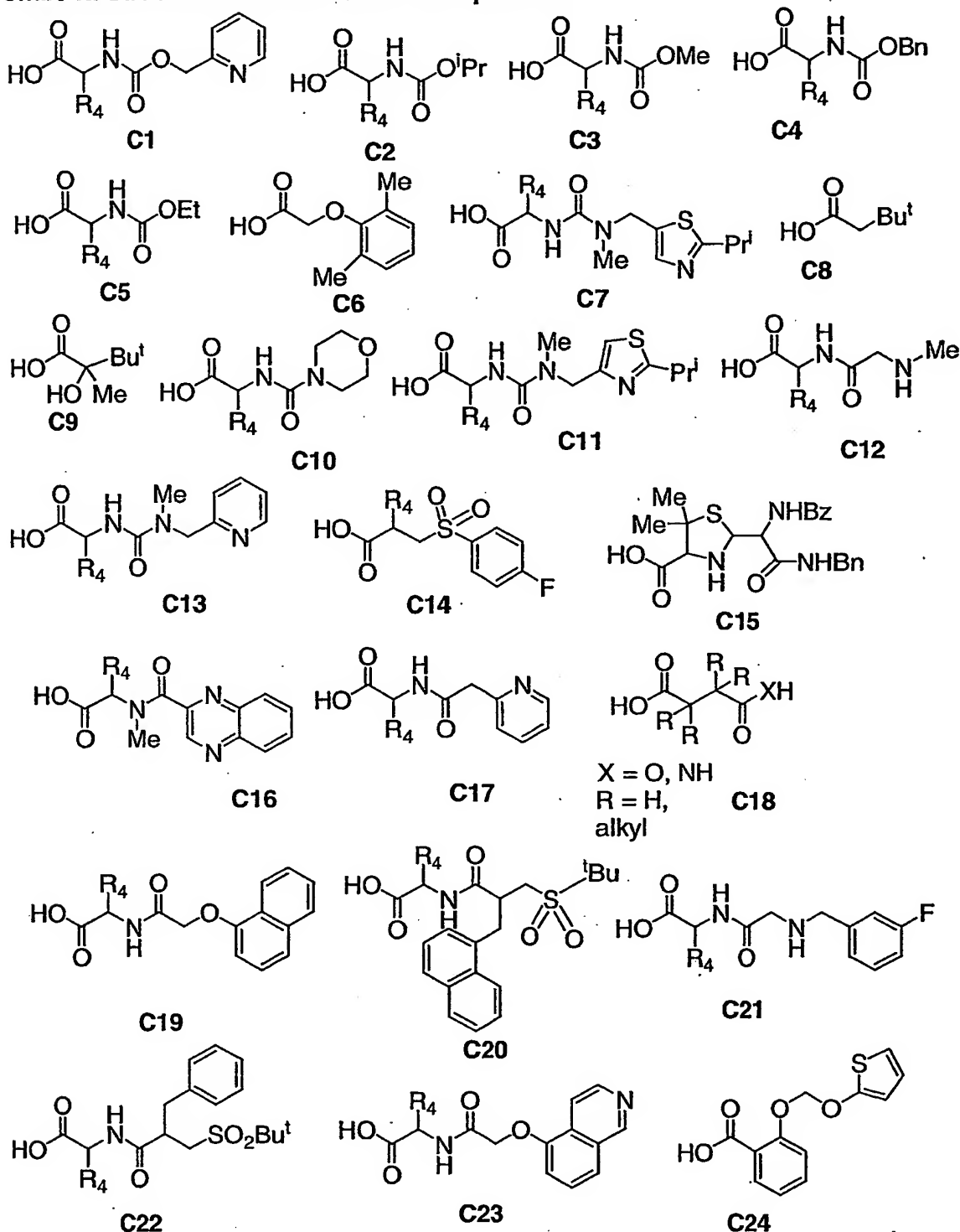
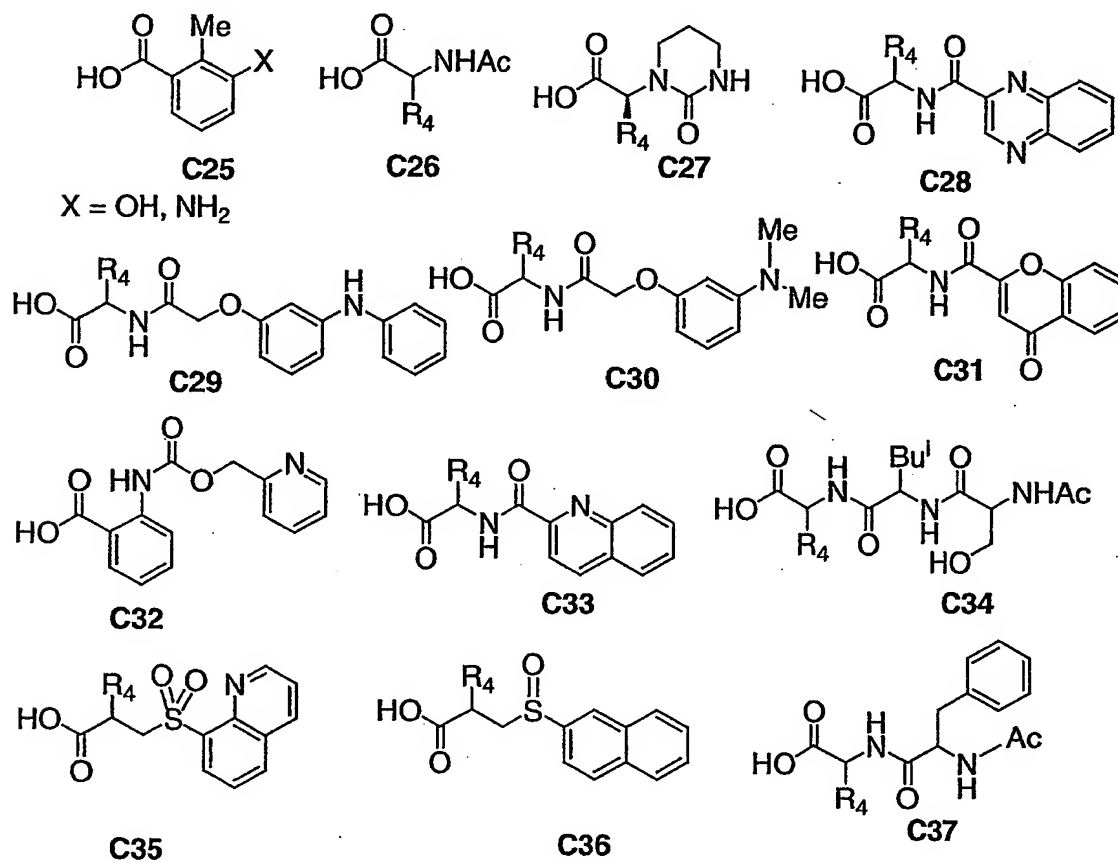
Chart 3. Structures of the R⁴ components

Chart 4a Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 4b Structures of the R⁵COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

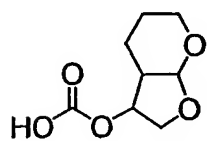
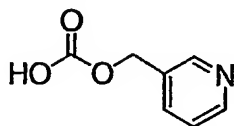
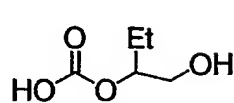
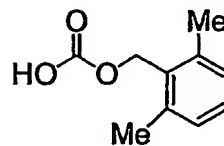
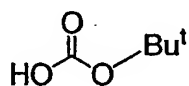
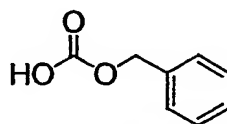
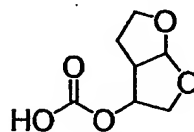
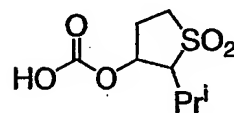
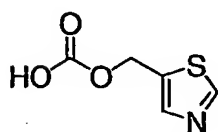
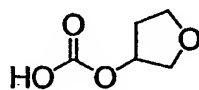
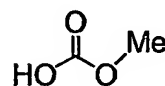
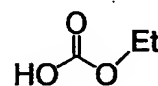
Chart 4c Structures of the R⁵COOH components**C38****C39****C40****C41****C42****C43****C44****C45****C46****C47****C48****C49**

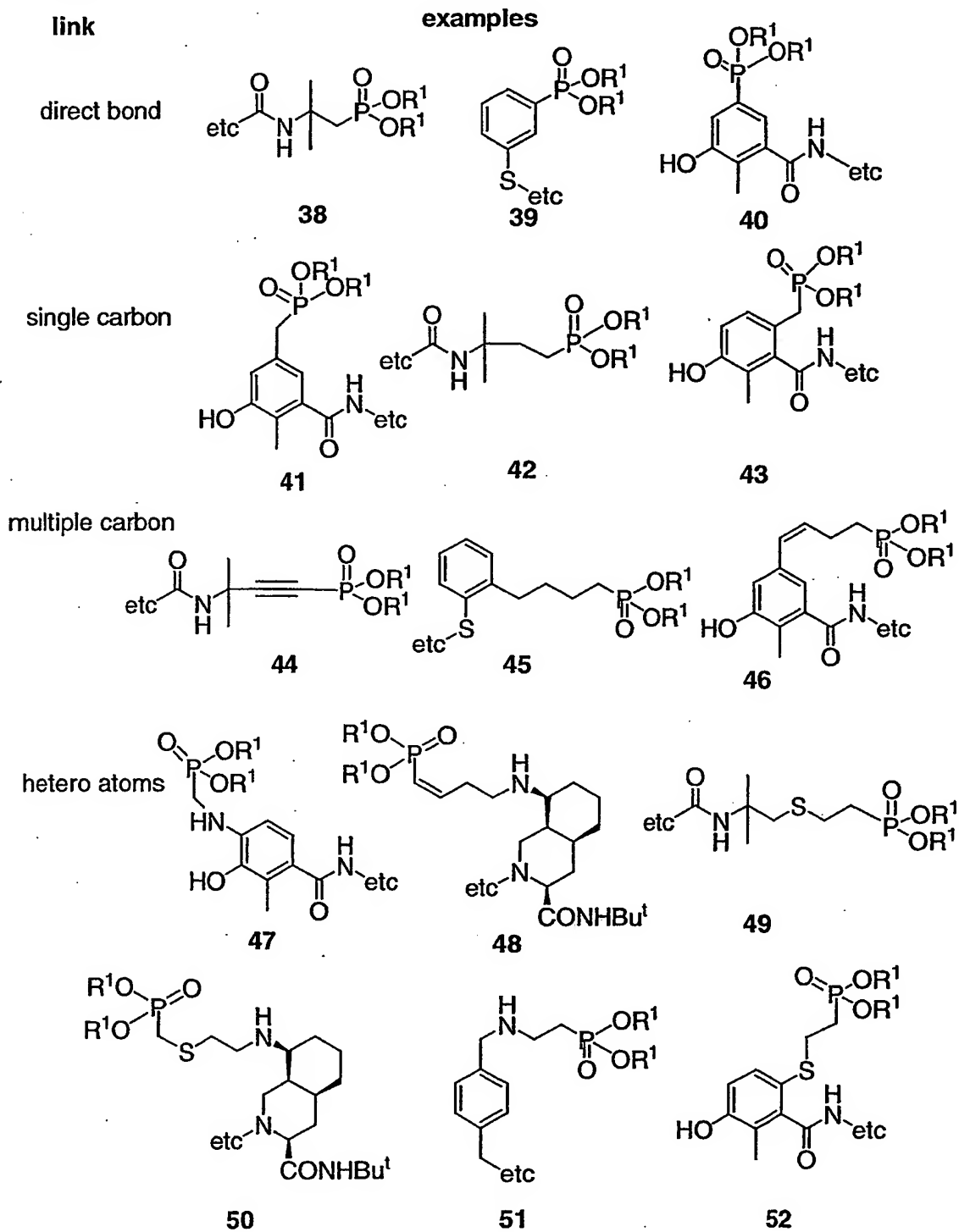
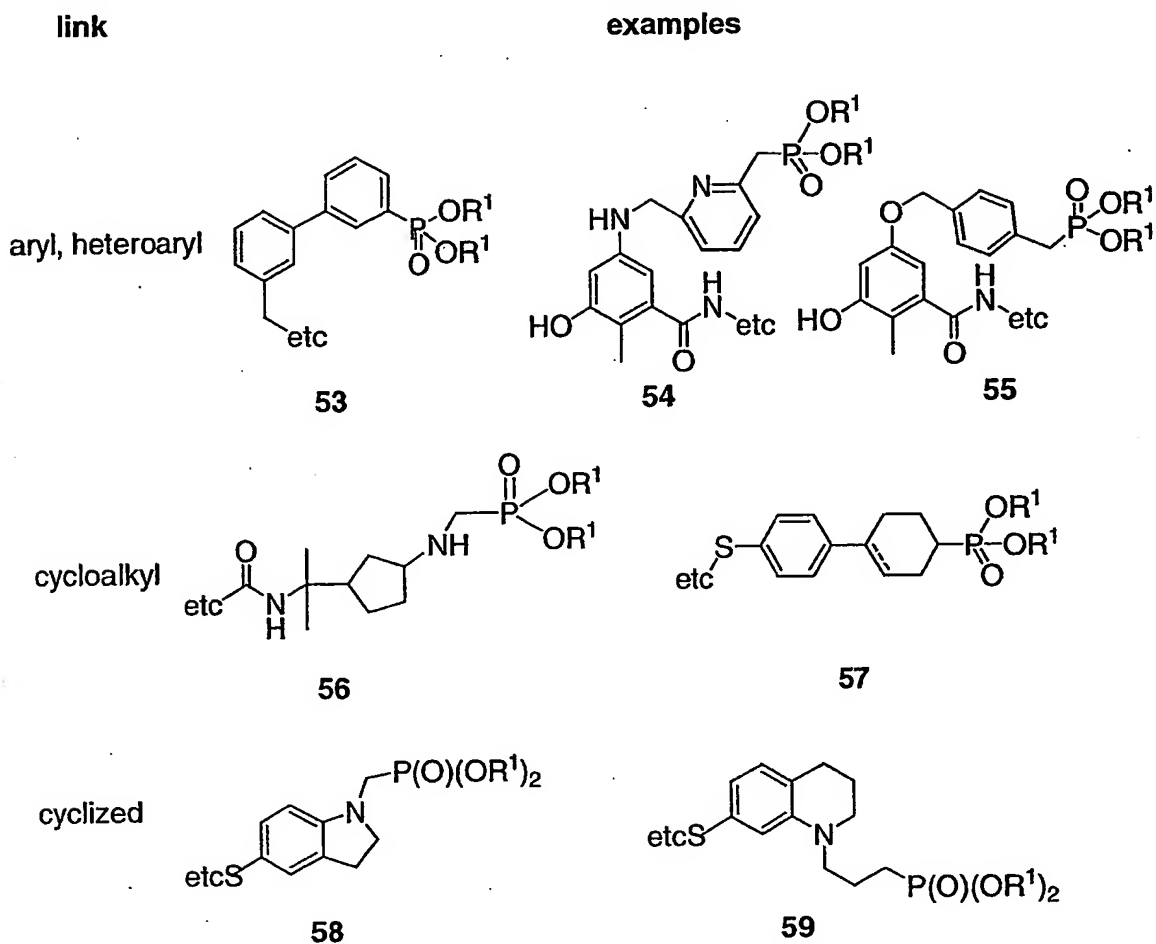
Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

Chart 5a Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990.

10 Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1, in which X=S.

The syntheses of the phosphonates 1 in which X=S, and in which the group link-P(O)(OR¹)₂ is attached to the benzoic acid moiety, are shown in Schemes 1- 3.

5 Scheme 1 illustrates the preparation of the phosphonate intermediate compounds 1, or precursors thereto. 4-Amino-tetrahydro-furan-3-ol 60, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with the carboxylic acid 61, or an activated derivative thereof, the preparations of which are described below, to form the amide 62.

10 The preparation of amides by reaction of carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

15 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

Preferably, the carboxylic acid is first converted into the acid chloride by reaction with, for example, thionyl chloride, oxalyl chloride and the like. The acid chloride 61, in which X is Cl, 20 is then reacted with an equimolar amount of the amine 60, in the presence of a weak inorganic base such as sodium bicarbonate, in an aprotic solvent such as dichloromethane, at ambient temperature, to afford the amide 62.

The hydroxyl group on the tetrahydrofuran moiety so obtained is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic 25 solvent such as pyridine or dichloromethane.

Preferably, the hydroxy amide 62 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 63.

30 The product 63, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 64. The rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst.

Preferably, the mesylate **63** is dissolved in an acylating agent such as acetic anhydride at about 0°, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate **64**.

The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine.

The compound **64** is reacted with an amine **5**, as defined in Chart 2, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product **65**.

Preferably, the mesylate compound **64** is reacted with an equimolar amount of the amine **5**, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product **65**.

The isoxazoline compound **65** is then reacted with a thiol R⁴SH **66**, in which R⁴ is phenyl, 4-fluorophenyl or 2-naphthyl, as shown in Chart 3, to afford the thioether **1**. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product **1**.

Preferably, the isoxazoline **65** is reacted, in methanol, with an equimolar amount of the thiol R⁴SH **66**, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether **1**.

Alternatively, the compounds **1** can be obtained by means of the reactions shown in Scheme 2. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, **67**, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R⁴SH **66**, as defined above, to afford the thioether **68**.

The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours, to afford **68**.

Preferably the mesylate **67** is reacted with an equimolar amount of the thiol R⁴SH **66**, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, to give the product **68**.

The 1,3-dioxolane protecting group present in the compound **68** is removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol **69**. Methods

for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G. M Wuts, Second Edition 1990, p. 191.

For example, the 1,3-dioxolane compound 68 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture.

- 5 Preferably, the 1,3-dioxolane 68 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the product 69.

The primary hydroxyl group of the diol 69 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as

- 10 dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol 69 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the ester 70.

- The hydroxy ester 70 is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 15 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester 71.

Preferably, equimolar amounts of the carbinol 70 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 71.

- The compound 71 is then subjected to a hydrolysis-cyclization reaction to afford the oxirane 20 72.

The mesylate or analogous leaving group present in 71 is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane 72 with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester 71 is reacted with an alkali metal hydroxide or tetraalkylammonium hydroxide in an aqueous organic

- 25 solvent.

Preferably, the mesylate 71 is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane 72.

The oxirane compound 72 is then subjected to regiospecific ring-opening reaction by treatment with an amine 5, to give the aminoalcohol 73.

- 30 The amine and the oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0° to 100°, and in the presence of an inorganic base, for 1 to 12 hours, to give the product 73.

Preferably, equimolar amounts of the reactants **5** and **72** are reacted in aqueous methanol at about 60° in the presence of potassium carbonate, for about 6 hours, to afford **73**.

The carbobenzyloxy (cbz) protecting group in the product **73** is removed to afford the free amine **74**. Methods for removal of cbz groups are described, for example, in Protective

5 Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Second Edition, p. 335.

The methods include catalytic hydrogenation and acidic or basic hydrolysis.

For example, the cbz-protected amine **73** is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine **74**.

10 Preferably, the cbz group is removed by the reaction of **73** with potassium hydroxide in an alcohol such as isopropanol at ca. 60° to afford the amine **74**.

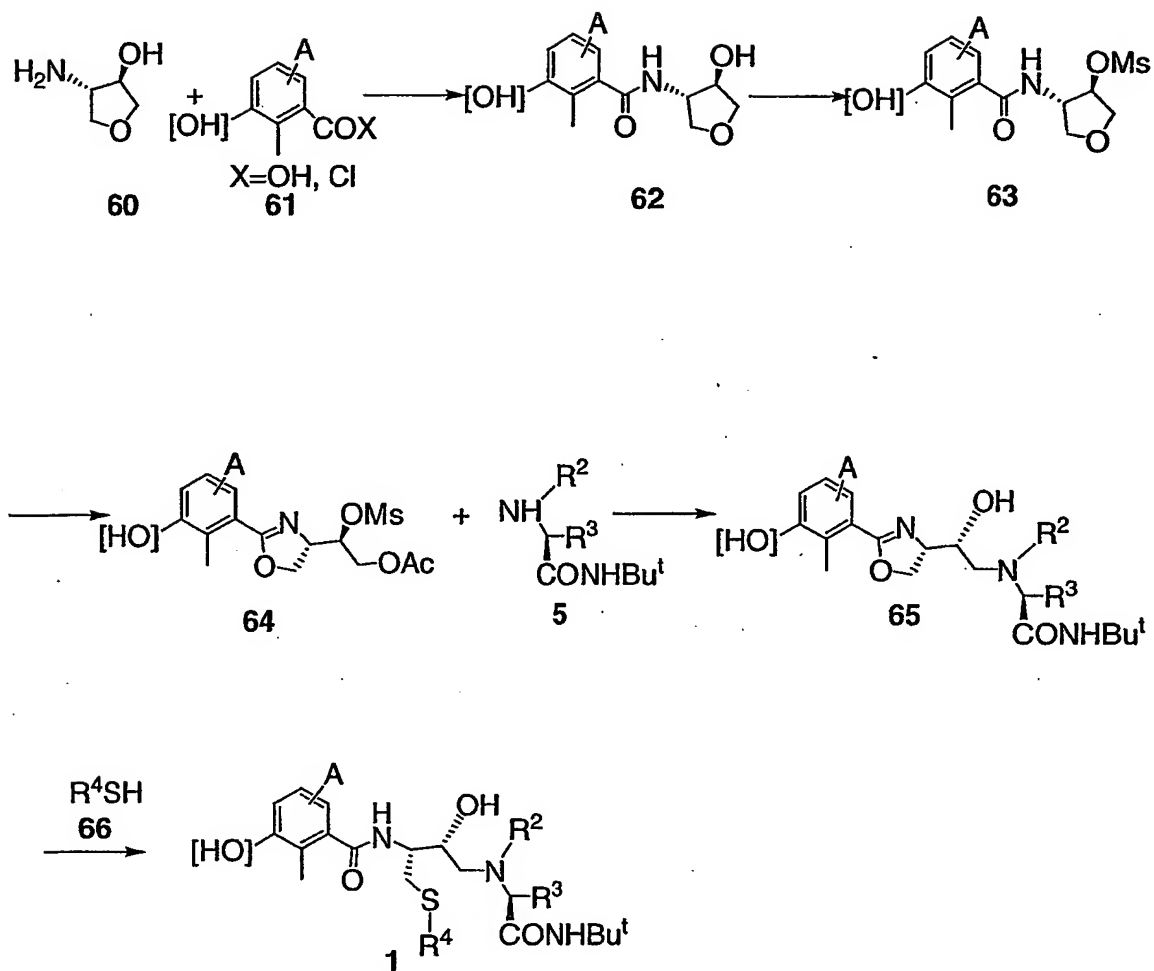
The amine **74** so obtained is next acylated with a carboxylic acid or activated derivative **61**, using the conditions described above for the conversion of **60** to **62**, to yield the final amide product **75**.

15 The reactions shown in the above-described Schemes 1 and 2 depict the preparation of intermediates **1** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 3 shows the conversion of the compounds **75** in which A is OH, SH, NH, to the compounds **1** in which A is link-P(O)(OR¹)₂.

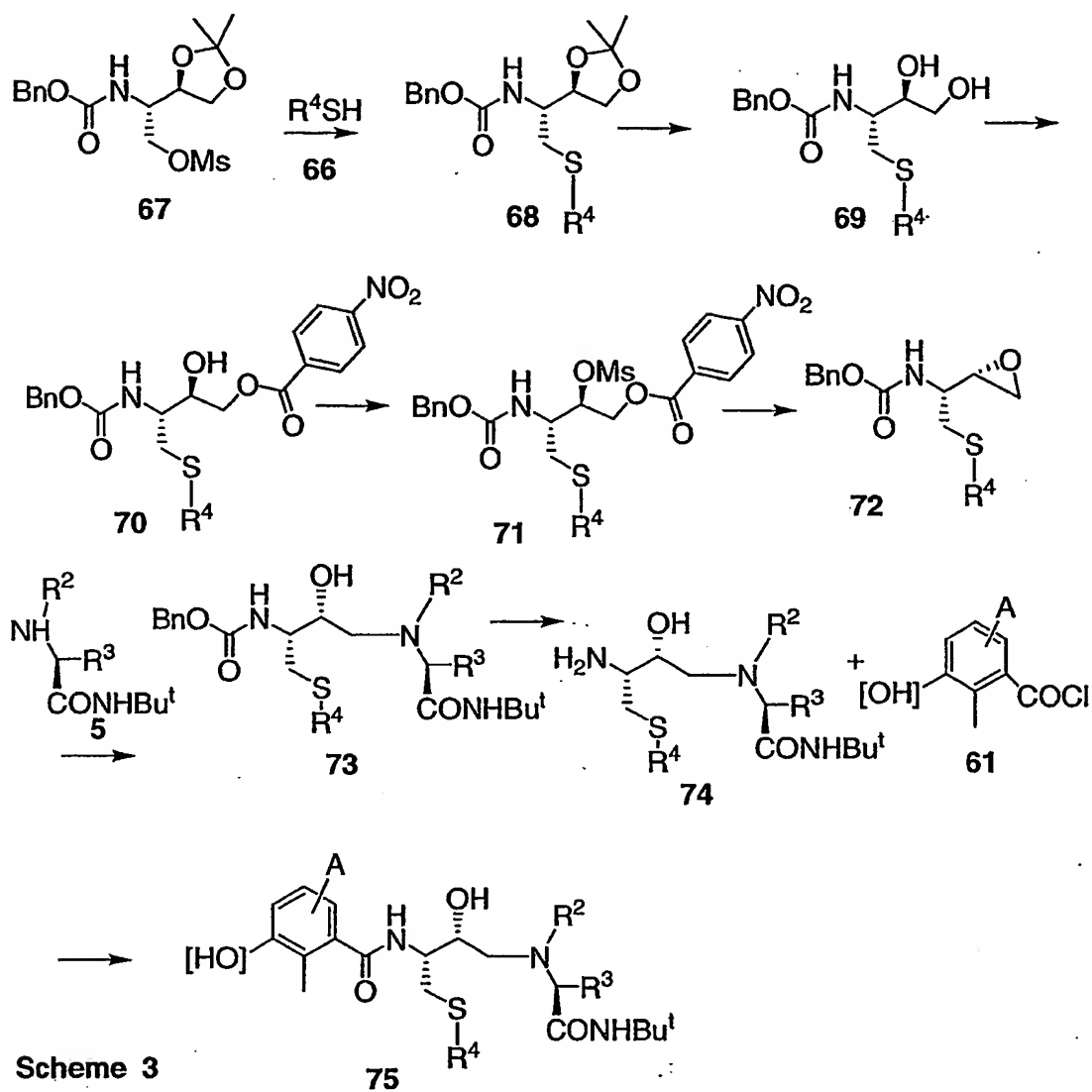
20 Methods for these transformations are described below, Schemes 20-48, in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 1

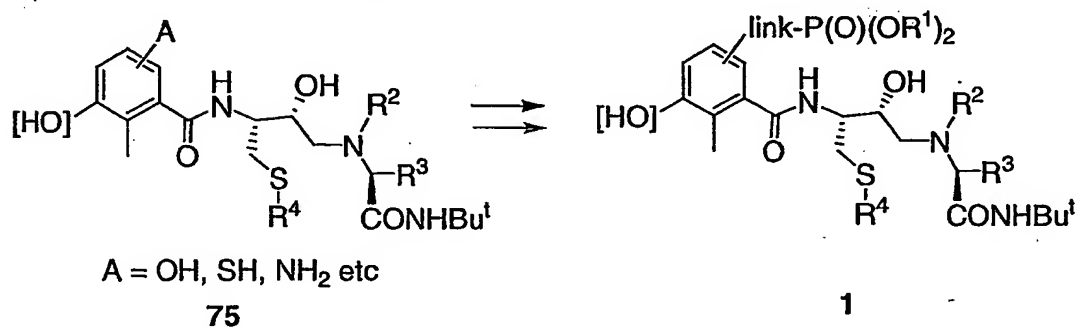


$\text{A} = \text{link}-(\text{P})(\text{OR}^1)_2$ or $\text{A} = \text{OH}, \text{SH}, \text{NH}, \text{etc}$

Scheme 2



Scheme 3



Preparation of the phosphonate intermediates 2, in which X = S.

The synthesis of the phosphonate compounds 2 in which the link-P(O)(OR¹)₂ group is attached to the phenylthio moiety, is shown in Scheme 4.

In this sequence, 4-amino-tetrahydro-furan-3-ol, 60, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R⁵COX, 76, using the conditions described above for the preparation of the amide 62, Scheme 1, to afford the amide 77. The compounds 77, and analogous acylation products described below, in which the carboxylic acid R⁵COOH is one of the carbonic acid derivatives C36-C49, as defined in Chart 4c, are carbamates. Methods for the preparation of carbamates are described below, (Scheme 50).

- 10 The amide product 77 is then transformed, using the sequence of reactions shown in Scheme 4, into the isoxazoline compound 80. The conditions for this sequence of transformations are the same as those described for the preparation of the isoxazoline 65 in Scheme 1.

The isoxazoline compound 80 is then reacted with a thiol compound 66, in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether 81.

The conditions for this reaction are the same as those described above for the preparation of the thioether 1, (Scheme 1).

- Alternatively, the thioether 81 can be prepared by the sequence of reactions shown in Scheme 5. In this sequence, the previously described 1,3-dioxolane mesylate compound 67 is reacted with a thiol compound 66 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor thereto, such as OH, SH, NH, as described herein, to afford the thioether 82. The conditions for this reaction are the same as those described above for the preparation of the thioether 68, (Scheme 2).

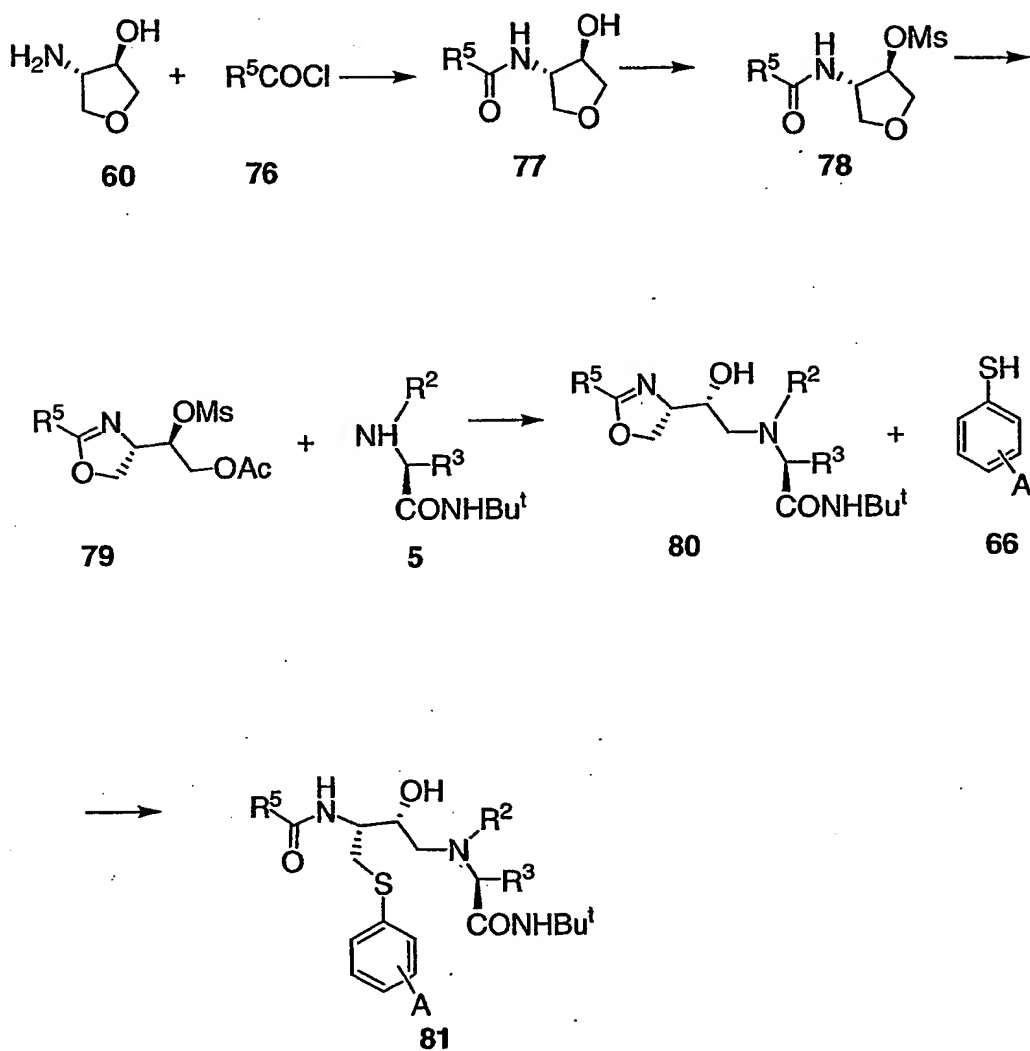
- 25 The thus-obtained thioether 82 is then transformed, using the sequence of reactions shown in Scheme 2 into the compound 81.

The reactions shown in the above-described Schemes 4 and 5 depict the preparation of intermediates 81 in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

- 30 Scheme 6 shows the conversion of the compounds 81 in which A is OH, SH, NH, into the compounds 2 in which A is link-P(O)(OR¹)₂.

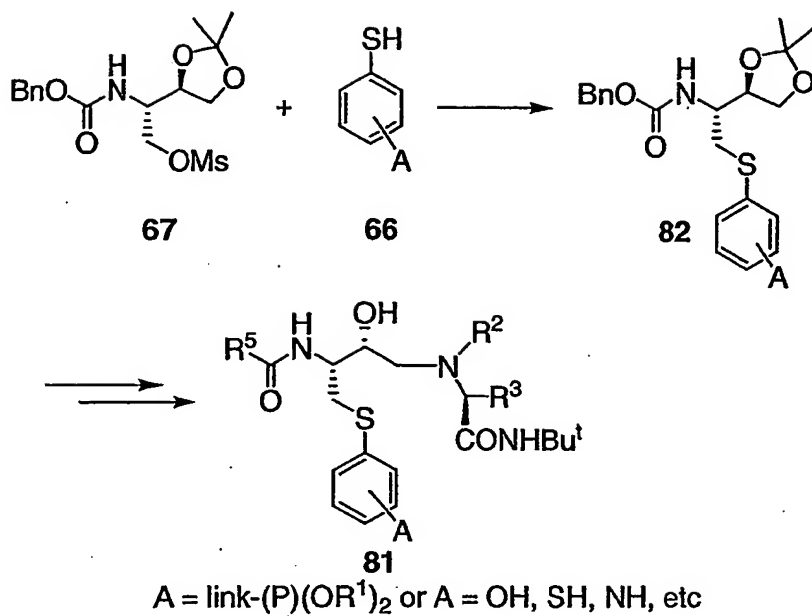
Methods for these transformations are shown in Schemes 20-48 and are discussed in the descriptions of the preparations of the phosphonate-containing reactants.

Scheme 4

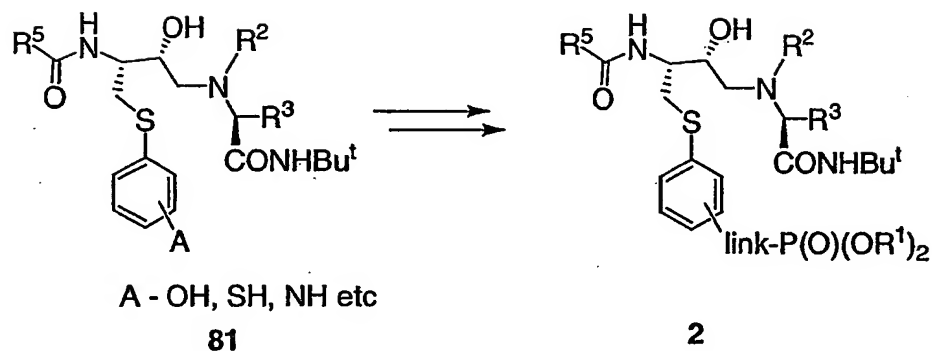


A = link-(P)(OR¹)₂ or A = OH, SH, NH, etc.

Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3, in which X = S.

The phosphonate intermediates 3 in which X = S, and in which the $\text{link-P}(\text{O})(\text{OR}^1)_2$ group is

5 attached to the tert. butyl moiety, are prepared as shown in Schemes 7 and 8.

As shown in Scheme 7, the isoxazolines **79**, the preparation of which are described above, are reacted with the amines **83**, using the conditions described above for the conversion of **64** to **65**, (Scheme 1) to afford the product **84**.

This compound is then converted, using the methods described above, (Scheme 1) into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compounds **85** can be prepared by the reactions shown in Scheme 8.

In this method, the oxirane **72**, the preparation of which is described above, (Scheme 2) is reacted with the amine **83**, using the reaction conditions described above for the conversion of **72** to **73** (Scheme 2), to afford the hydroxyamine **86**. This compound is then converted, using the procedures described above, into the compound **85**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes 7 and 8 depict the preparation of intermediates **85** in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 9 shows the conversion of the compounds **85** in which A is OH, SH, NH, into the compounds **3** in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20 to 48 in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 4 in which X = S.

The preparations of the phosphonate intermediates **4**, in which the link-P(O)(OR¹)₂ group is attached to the decahydroisoquinoline moiety, are shown in Schemes 10 to 12.

As shown in Scheme 10, the isoxazoline mesylate **79**, the preparation of which is described above, (Scheme 4) is reacted with the amine **88**, the preparation of which is described below. The reaction is preformed using the procedures described above for the preparation of **65** (Scheme 1).

The reaction product **89** is then transformed, using the procedures described above, (Scheme 1) into the compound **90**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Alternatively, the compound **90** can be prepared by the reactions shown in Scheme 11.

In this reaction scheme, the oxirane 72, the preparation of which is described above, (Scheme 2) is reacted with the amine 88, using the conditions described above for the preparation of 73 (Scheme 2) to afford the hydroxyamine 91. This compound is then converted, using the reaction schemes and conditions described above for the preparation of 1, (Scheme 2) into the compound 90, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

The reactions shown in the above-described Schemes 10 and 11 depict the preparation of intermediates 90 in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

- 10 Scheme 12 shows the conversion of the compounds 90 in which B is OH, SH, NH, to the compounds 4 in which A is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

15 **Preparation of the phosphonate intermediates 1, in which X is a direct bond**

As shown in Scheme 13, the oxirane 92, in which X is H, the preparation of which is described in J. Med. Chem., 1997, 40, 1995, and in Bioorg. Med. Chem. Lett., 5, 2885, 1995, is reacted with the amine 5. The compounds are reacted together using the conditions described above for the preparation of 73, (Scheme 2) to afford the hydroxyamine 93. This compound is then transformed, using the procedures described above for the preparation of 1, (Scheme 2) into the compound 94, in which A is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 14 shows the conversion of the compounds 94 in which A is OH, SH, NH, to the compounds 1 in which A is link-P(O)(OR¹)₂.

- 25 Methods for these transformations are described below in Schemes 20-43 in which the preparations of the phosphonate-containing reactants are depicted.

Preparation of the phosphonate intermediates 2, in which X is a direct bond.

- The preparation of the compounds 2, in which X is a direct bond, and the group link-P(O)(OR¹)₂ is attached to the phenyl ring, is illustrated in Schemes 14a and 14b.
- 30

In the procedure shown in Scheme 14a, the epoxide 14a-1, prepared as described below (Scheme 45) is reacted with an amine 5, using the conditions described above for the preparation of the hydroxyamine 73 (Scheme 2), to afford the hydroxyamine 14a-2.

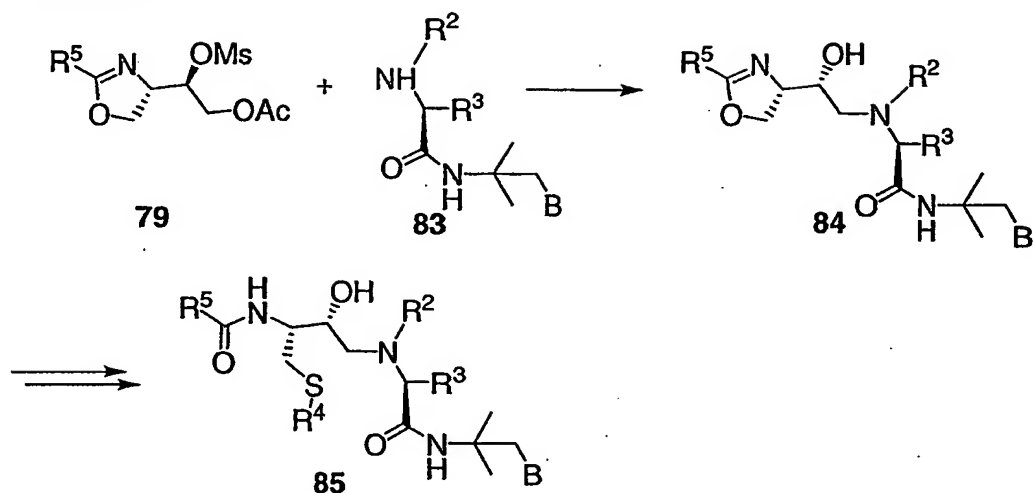
The latter compound, after removal of the BOC protecting group as described in Protective

- 5 Groups in Organic Synthesis, by T.W. Greene and P.G. M. Wuts, Third Edition 1999, p. 520-522, is then converted, by reaction with the carboxylic acid R^5COOH , or an activated derivative thereof, into the amide 14a-3. The conditions for this reaction are the same as those described above for the preparation of the amide 62, (Scheme 1).

- 10 The reactions shown in Scheme 14a illustrate the preparation of the compounds 14a-3 in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto such as OH, SH, NH_2 . Scheme 14b illustrates the conversion of the compounds 14a-3, in which A is OH, SH, NH_2 , into the compounds 2 in which A is the group $link-P(O)(OR^1)_2$. The methods for this transformation are described below in Schemes 20-48, in which the preparation of the phosphonate-containing reactants are described.

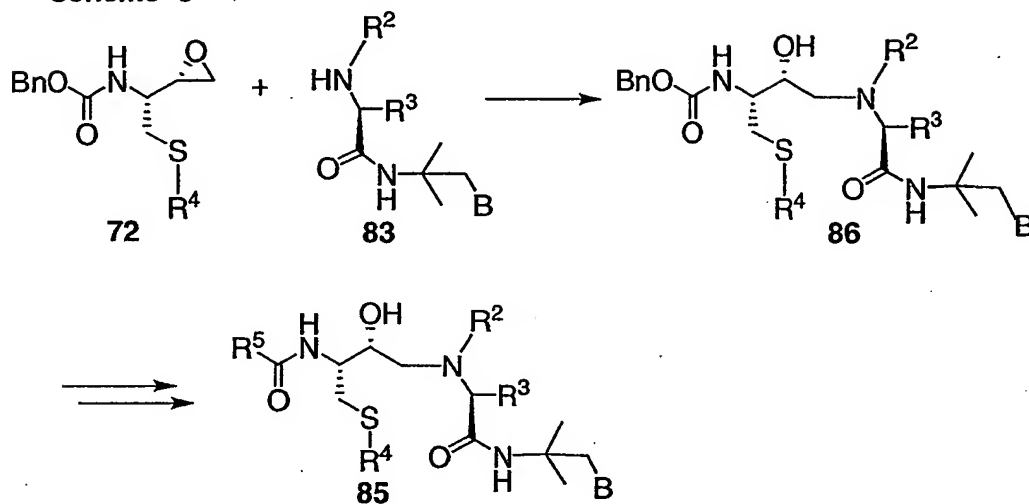
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Scheme 7



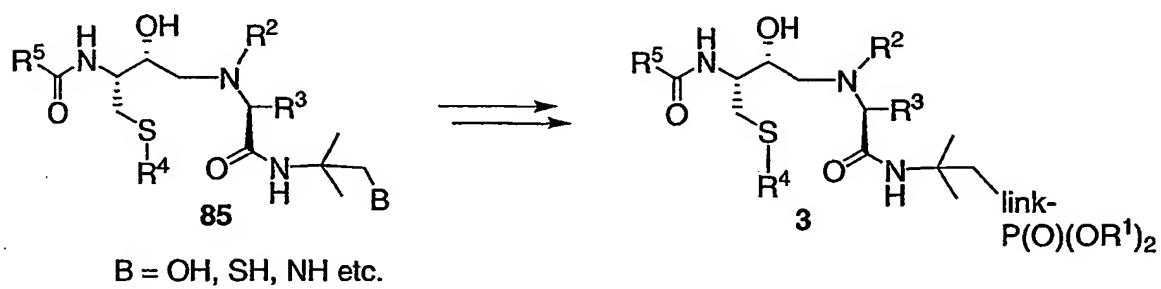
$B = \text{link}-(P)(OR^1)_2$ or $B = OH, SH, NH$ etc.

Scheme 8



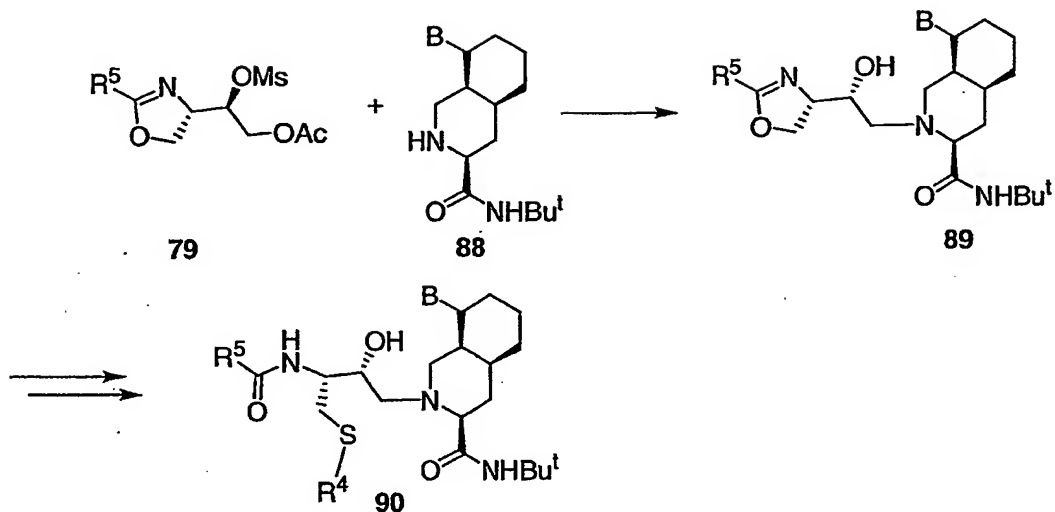
$B = \text{link}-(P)(OR^1)_2$ or $B = OH, SH, NH$ etc.

Scheme 9



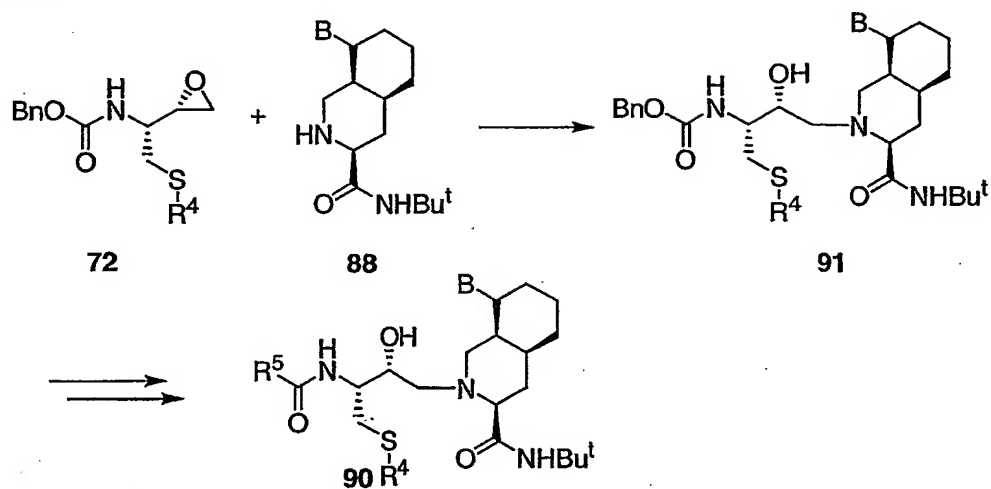
$B = OH, SH, NH$ etc.

Scheme 10



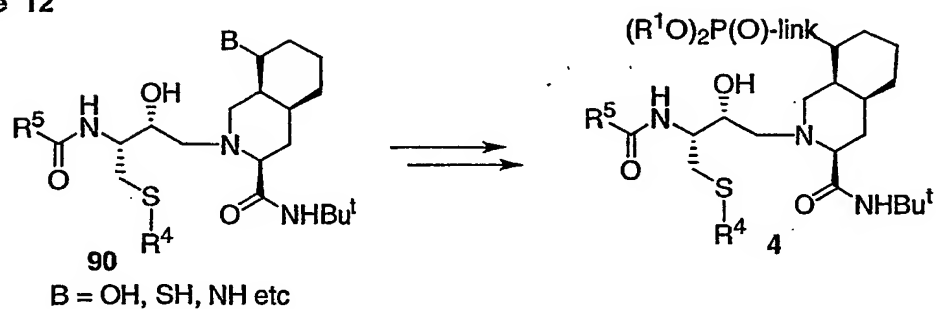
B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

Scheme 11



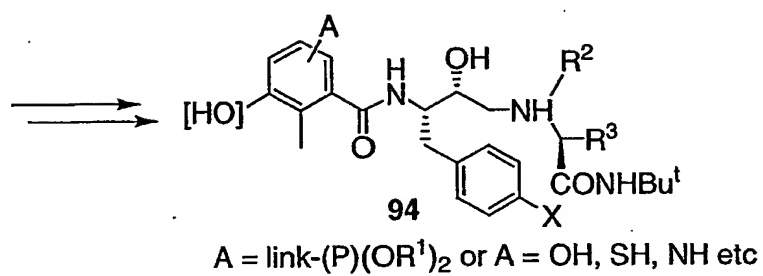
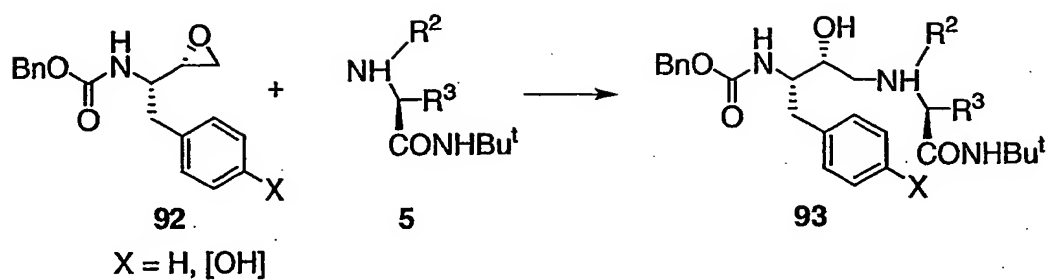
B = link-(P)(OR¹)₂ or B = OH, SH, NH etc

Scheme 12

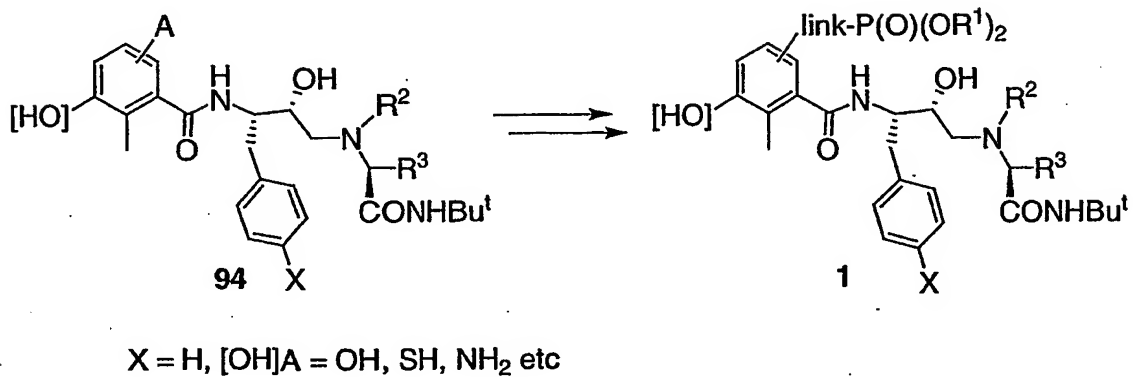


B = OH, SH, NH etc

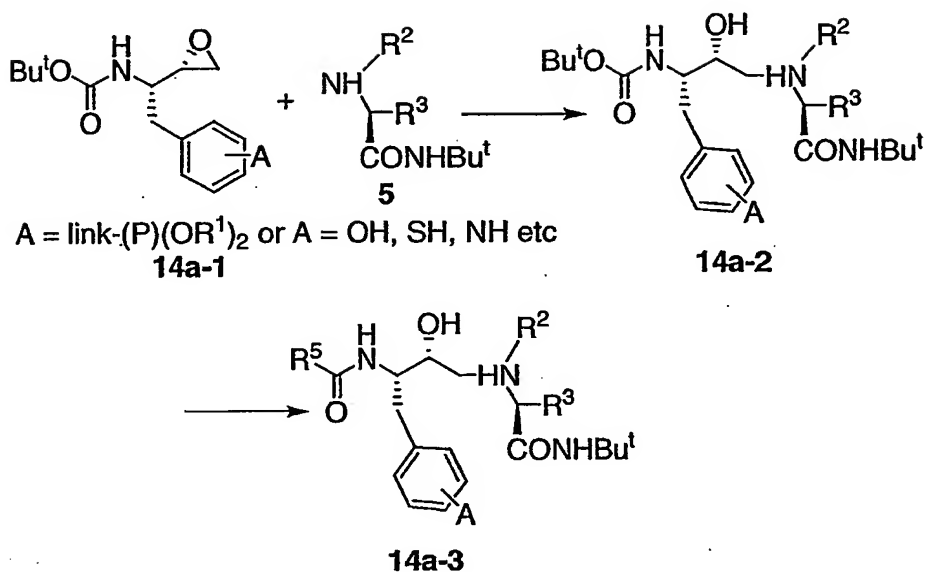
Scheme 13



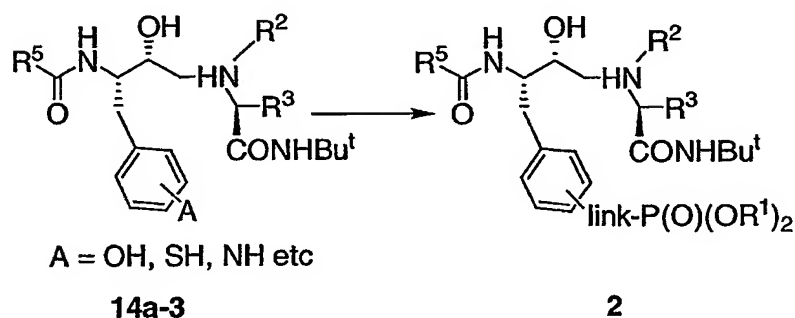
Scheme 14



Scheme 14a



Scheme 14b



Preparation of the phosphonate intermediates 3, in which X is a direct bond.

As shown in Scheme 15, the oxirane **92**, in which X is H, is reacted with the amine **83**, in which the phosphonate or precursor group is attached to the tert. butyl group, to afford the product **95**. The conditions for this reaction are the same as described above for the preparation of **73** (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of **1**, (Scheme 2) into the compound **96**, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

Scheme 16 shows the conversion of the compounds 96 in which B is OH, SH, NH, to the compounds 3 in which B is link-P(O)(OR¹)₂.

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

5

Preparation of the phosphonate intermediates 4, in which X is a direct bond.

As shown in Scheme 17, the oxirane 92 is reacted with the amine 88, in which the phosphonate or precursor group is attached to the decahydroisoquinoline moiety, to afford the product 97. The conditions for this reaction are the same as described above for the preparation of 73 (Scheme 2). This compound is then transformed, using the procedures described above for the preparation of 1, (Scheme 2) into the compound 98, in which B is either link-P(O)(OR¹)₂ or precursor groups to link-P(O)(OR¹)₂ such as OH, SH, NH, as described herein.

10

Scheme 18 shows the conversion of the compounds 98 in which B is OH, SH, NH, into the compounds 4 in which B is link-P(O)(OR¹)₂.

15

Methods for these transformations are described below in Schemes 20-48 in which the preparations of the phosphonate-containing reactants are depicted.

Schemes 13-18 illustrate the preparations of the compounds 1, 3 and 4, in which X is a direct bond, and in which the phenyl ring is either unsubstituted or incorporates a protected hydroxyl group at the 4-position.

20

Scheme 19 depicts the synthesis of compounds 1, 3 and 4, in which X is a direct bond, and in which the phenyl ring incorporates different substituents, as described above (Chart 3) in the 4-position.

In this procedure, [2-(4-hydroxy-phenyl)-1-oxiranyl-ethyl]-carbamic acid tert-butyl ester 99, the preparation of which is described in U.S. Patent 5,492,910, is reacted with an appropriate alkylating agent, such as, for example, ethyl iodide, benzyl chloride, bromoethyl morpholine or bromoacetyl morpholine. The reaction is conducted in an aprotic solvent, such as, for example, dichloromethane or dimethylformamide, in the presence of an organic or inorganic base.

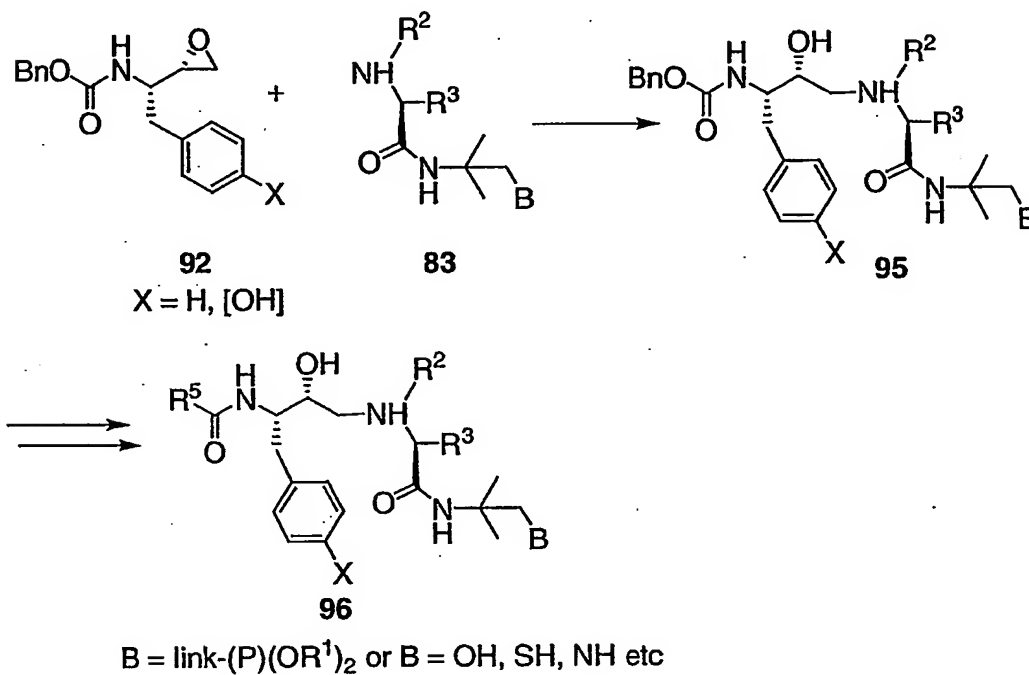
25

Preferably the hydroxy compound 99 is reacted with an equimolar amount of the alkylating agent in dichloromethane, in the presence of diisopropylethylamine, at ambient temperature, so as to afford the ether products 100. The compounds 100 are then transformed, using the

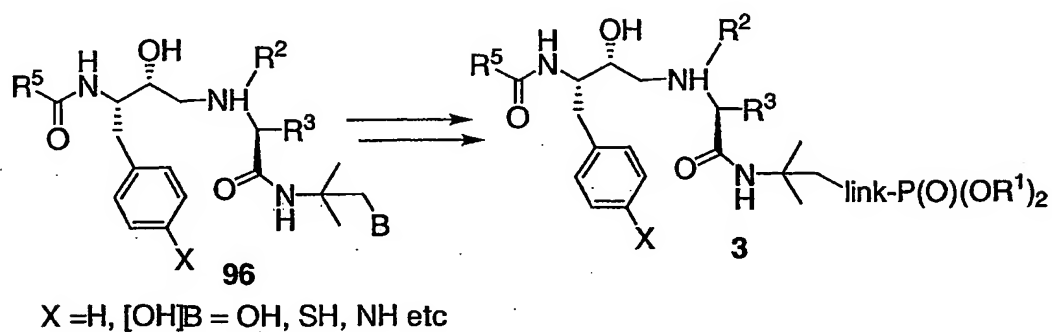
30

conditions described above for the reactions depicted in Schemes 13-18, into the products 1, 3 and 4, in which X is a direct bond, and in which R is as defined in Scheme 19.

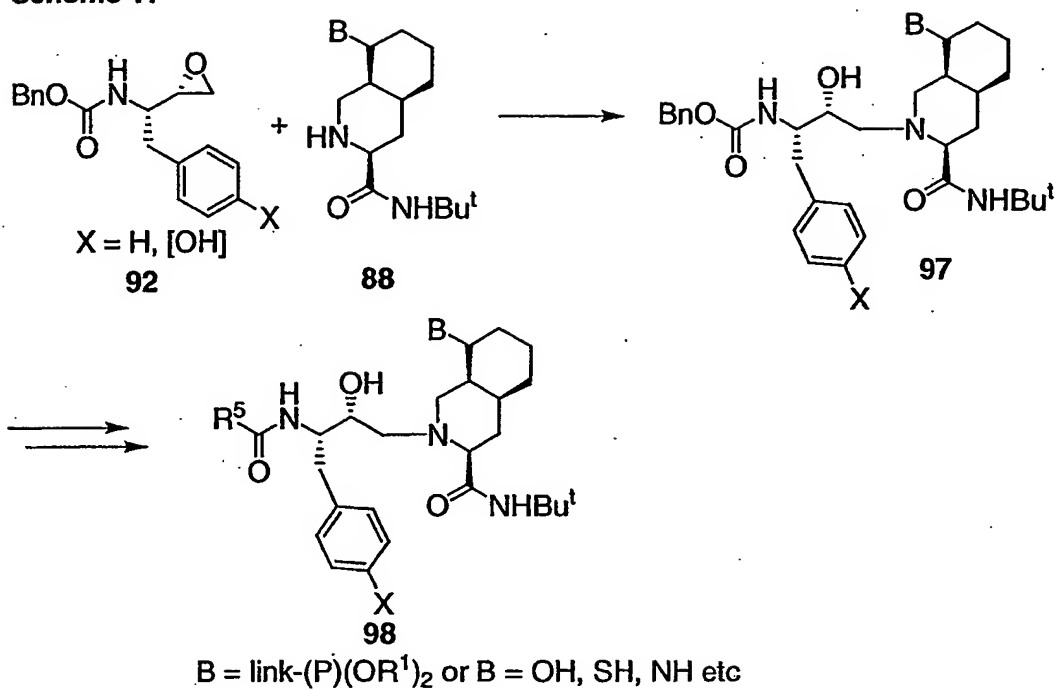
Scheme 15



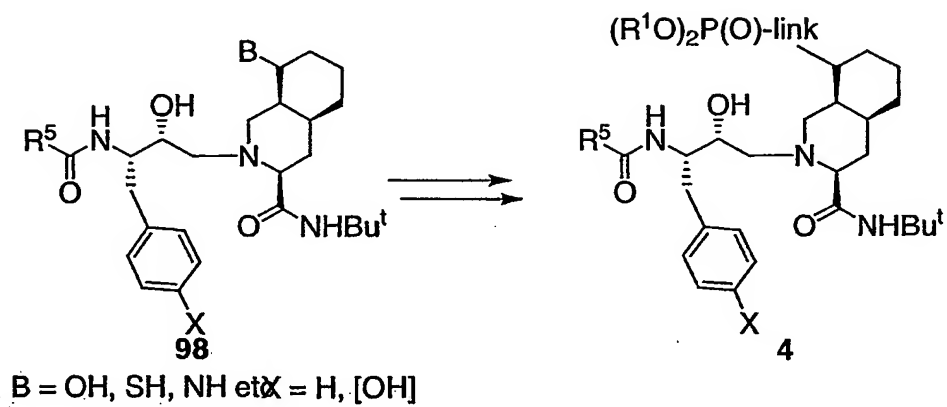
Scheme 16



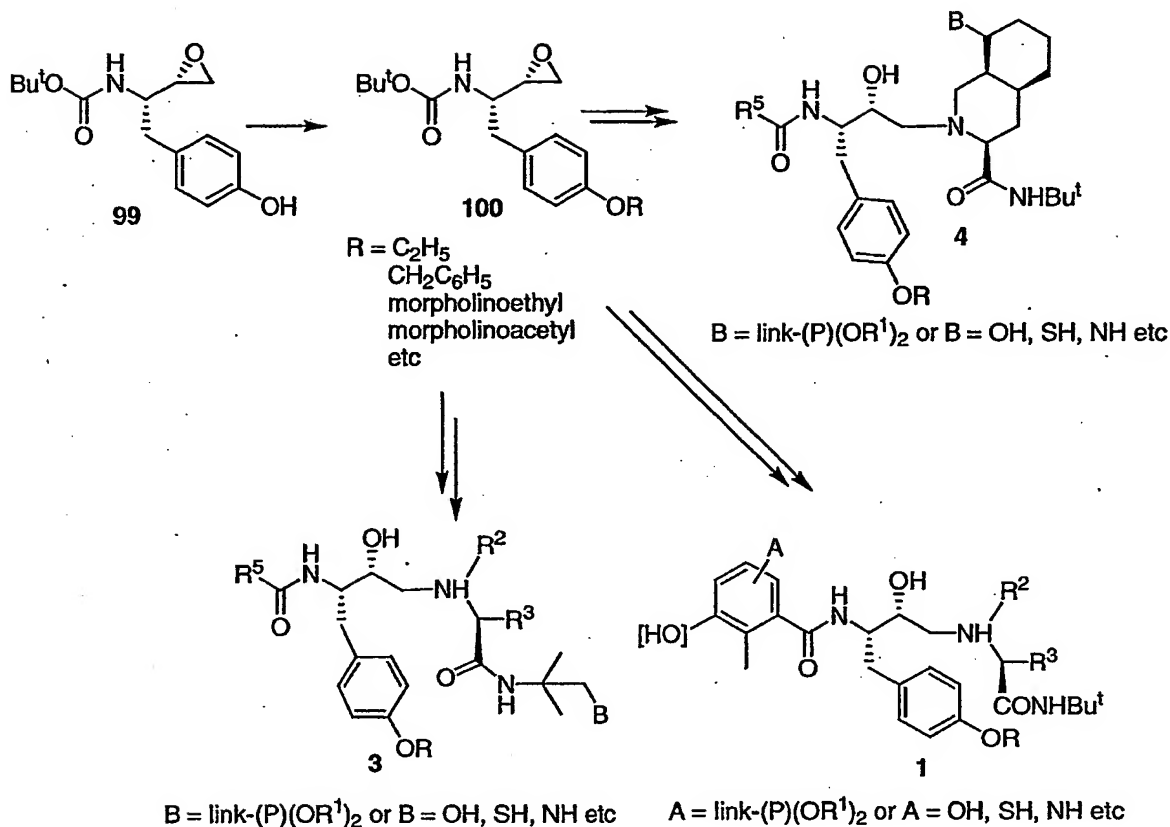
Scheme 17



Scheme 18



Scheme 19



Nel10b.cdx Schemes 19a, 19b

5 Preparation of thiophenol derivatives R^4SH incorporating phosphonate substituents

Various methods for the preparation of thiols are described in *The Chemistry of the Thiol Group*, S. Patai, Ed., Wiley, 1974, Vol. 14, Part 3, p 42.

10 Protection/deprotection of SH groups.

The preparations of thiophenols incorporating phosphonate moieties are shown in Schemes 20-30. In order to avoid unwanted reactions, it may be necessary to protect the SH group, and to deprotect it after the transformations shown. Protected SH groups are shown in the Schemes as [SH]. The protection and deprotection of SH groups is described in a number of publications. For example, in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 277-308, are described the introduction and removal of a

number of SH protecting groups. The selection of a SH protecting group for a given series of reactions requires that it be stable to the reaction conditions employed, and that the protecting group can be removed at the end of the reaction sequence without the occurrence of undesired reactions. In the following descriptions, appropriate protection and deprotection methods are indicated.

Scheme 20 illustrates the preparation of thiophenols in which a phosphonate moiety is attached directly to the aromatic ring.

In this procedure, a halo-substituted thiophenol is subjected to a suitable protection procedure.

10 The protected compound **101** is then coupled, under the influence of a transition metal catalyst, with a dialkyl phosphite **102**, to afford the product **103**. The product is then deprotected to afford the free thiophenol **104**.

Suitable protecting groups for this procedure include alkyl groups such as triphenylmethyl and the like. Palladium (0) catalysts are employed, and the reaction is conducted in an inert
15 solvent such as benzene, toluene and the like, as described in J. Med. Chem., 35, 1371, 1992. Preferably, the 3-bromothiophenol **105** is protected by conversion to the 9-fluorenylmethyl derivative, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 284, and the product **106** is reacted in toluene with a dialkyl phosphite in the presence of tetrakis(triphenylphosphine)palladium (0) and triethylamine, to
20 yield the product **108**. Deprotection, for example by treatment with aqueous ammonia in the presence of an organic co-solvent, as described in J. Chem. Soc. Chem. Comm. 1501, 1986, then gives the thiol **109**.

Using the above procedures, but employing, in place of the bromo compound **105**, different bromo compounds **101**, there are obtained the corresponding thiols **104**.

25

Scheme 21 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol **101** is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative **110**. The latter compound is reacted
30 with a halodialkyl phosphate **111** to afford the product **103**.

Preferably, the 4-bromothiophenol **112** is converted into the S-triphenylmethyl (trityl) derivative **113**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **114** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodiethyl phosphite **115** to afford the phosphonate **116**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **117**.
Using the above procedures, but employing, in place of the halo compound **112**, different halo compounds **101**, there are obtained the corresponding thiols **104**.

Scheme 22 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link.

In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **118**. This compound is reacted with a sodium dialkyl phosphite **119** or a trialkyl phosphite, to give the displacement or rearrangement product **120**, which upon deprotection affords the thiophenols **121**.

Preferably, 2-methylthiophenol **123** is protected by conversion to the benzoyl derivative **124**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **125**. This material is reacted with a sodium dialkyl phosphite **119**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **126**. Alternatively, the bromomethyl compound **125** can be converted into the phosphonate **126** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **125** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **126**. Deprotection of **126**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **127**.

Using the above procedures, but employing, in place of the bromomethyl compound **125**, different bromomethyl compounds **118**, there are obtained the corresponding thiols **121**.

Scheme 23 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **128** is reacted with a dialkyl hydroxyalkylphosphonate **129** under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42,

335, to afford the coupled product 130. Deprotection then yields the O- or S-linked products 131.

Preferably, the substrate, for example 3-hydroxythiophenol, 132, is converted into the monotrityl ether 133, by reaction with one equivalent of trityl chloride, as described above.

5 This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 134 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 135. Removal of the trityl protecting group, as described above, then affords the thiophenol 136.

Using the above procedures, but employing, in place of the phenol 132, different phenols or
10 thiophenols 128, there are obtained the corresponding thiols 131.

Scheme 24 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 137 is reacted with an activated ester, for example the trifluoromethanesulfonate, of a dialkyl hydroxyalkyl phosphonate 138, to afford the coupled
15 product 139. Deprotection then affords the thiol 140.

For example, the substrate, 4-methylaminothiophenol 141, is reacted with one equivalent of acetyl chloride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 142. This material is then reacted with, for example, diethyl trifluoromethanesulfonylmethyl phosphonate 143, the preparation of
20 which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 144.

Preferably, equimolar amounts of the phosphonate 143 and the amine 142 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 144. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Amer.
25 Chem. Soc., 85, 1337, 1963, then affords the thiophenol 145.

Using the above procedures, but employing, in place of the thioamine 142, different phenols, thiophenols or amines 137, and/or different phosphonates 138, there are obtained the corresponding products 140.

Scheme 25 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 146.

5 In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 137 is reacted with a dialkyl bromoalkyl phosphonate 146 to afford the product 147. Deprotection then affords the free thiophenol 148.

For example, 3-hydroxythiophenol 149 is converted into the S-trityl compound 150, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 151, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction
10 is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 152. Deprotection, as described above, then affords the thiol 153.

15 Using the above procedures, but employing, in place of the phenol 149, different phenols, thiophenols or amines 137, and/or different phosphonates 146, there are obtained the corresponding products 148.

Scheme 26 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by
20 means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 155 is coupled with an aromatic bromo compound 154. In this procedure, a suitably protected bromo-substituted thiophenol 154 is reacted with a terminally unsaturated phosphonate 155, to afford the coupled product 156. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 157, or the
25 saturated analog 159.

For example, 3-bromothiophenol is converted into the S-Fm derivative 160, as described above, and this compound is reacted with diethyl 1-butenyl phosphonate 161, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med.
30 Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for

example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 162. Deprotection, as described above, then affords the thiol 163.

Optionally, the initially formed unsaturated phosphonate 162 can be subjected to catalytic hydrogenation, using, for example, palladium on carbon as catalyst, to yield the saturated product 164, which upon deprotection affords the thiol 165.

Using the above procedures, but employing, in place of the bromo compound 160, different bromo compounds 154, and/or different phosphonates 155, there are obtained the corresponding products 157 and 159.

- 10 Scheme 28 illustrates the preparation of an aryl-linked phosphonate ester 169 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57.

- 15 The sulfur-substituted phenylboronic acid 166 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 168 which is deprotected to yield the thiol 169.

- For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in
20 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 170. This material is reacted with diethyl 4-bromophenylphosphonate 171, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium
25 (0) and an inorganic base such as sodium carbonate, to afford the coupled product 172. Deprotection, for example by the use of tetrabutyl ammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 173.

Using the above procedures, but employing, in place of the boronate 170, different boronates 166, and/or different phosphonates 167, there are obtained the corresponding products 169.

Scheme 29 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring.

In this procedure, a suitably protected O, S or N-substituted thiophenol 137 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 174, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 175 is then deprotected to afford the thiol 176. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester 177 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 177 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 178, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 179 thus obtained is deprotected, as described above, to afford the thiol 180.

Using the above procedures, but employing, in place of the thiophenol 177, different phenols, thiophenols or amines 137, and/or different phosphonates 174, there are obtained the corresponding products 176.

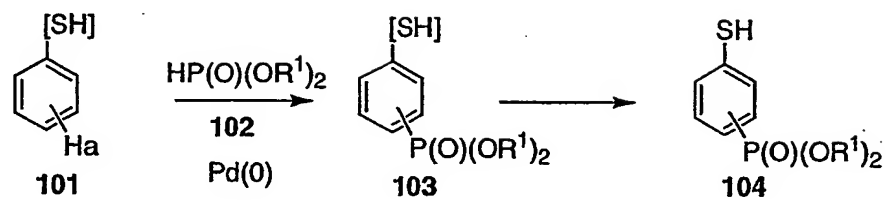
Scheme 30 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol 181, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 138, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 182. Deprotection, as described above, then affords the thiol 183. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

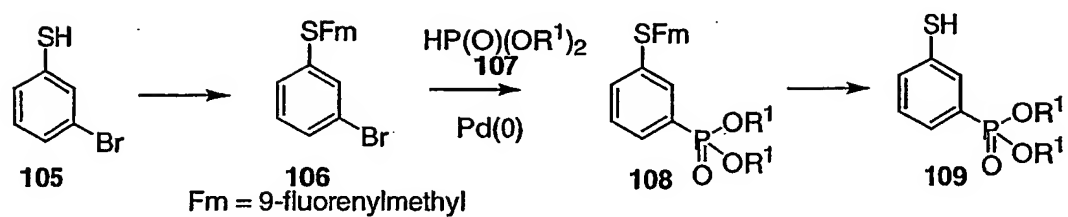
J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic
5 Functional Group Preparations, A. R. Katritzky et al., eds., Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, **184**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **185**, as described above, and the ester is then reacted with the triflate **143**, using the conditions described above for the preparation of **144**, (Scheme 24), to yield the phosphonate **186**. Deprotection, for example by reaction with dilute
10 aqueous ammonia, as described above, then affords the thiol **187**. Using the above procedures, but employing, in place of the thiol **184**, different thiols **181**, and/or different triflates **138**, there are obtained the corresponding products **183**.

Scheme 20

Method

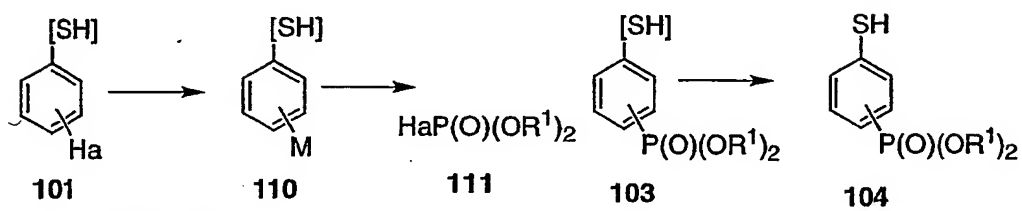


Example

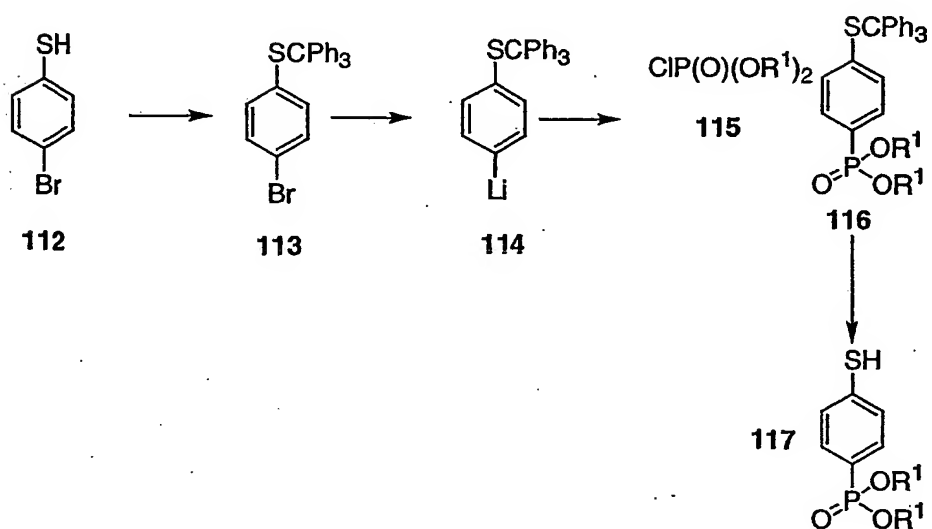


Scheme 21

Method

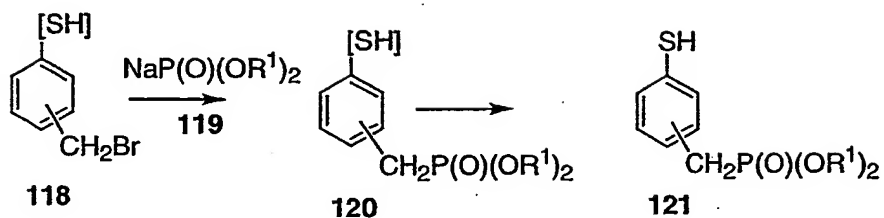


Example

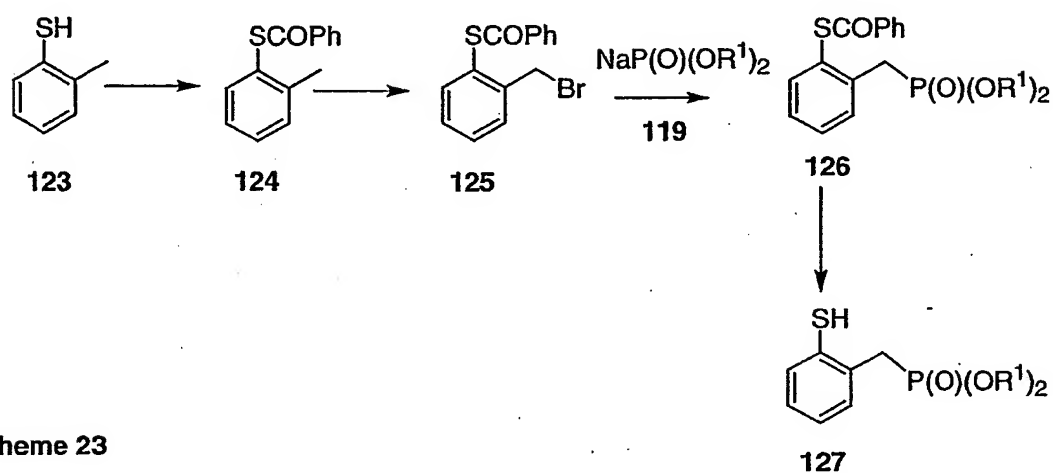


Scheme 22

Method

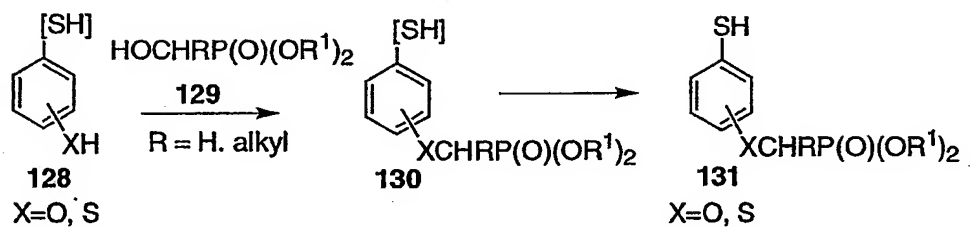


Example

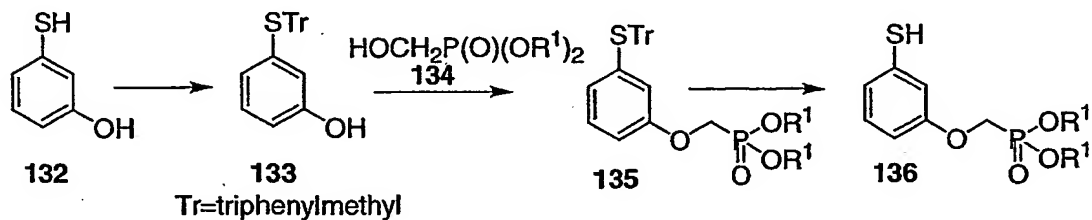


Scheme 23

Method

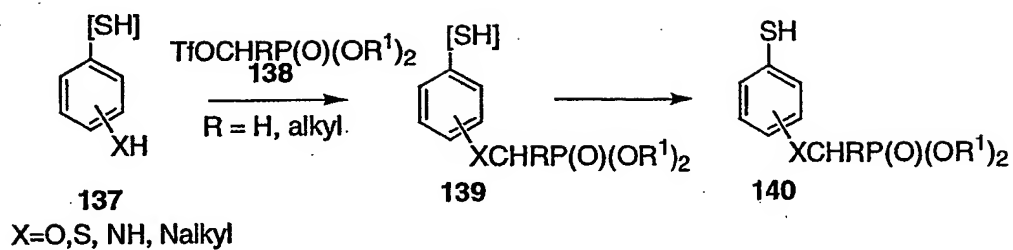


Example

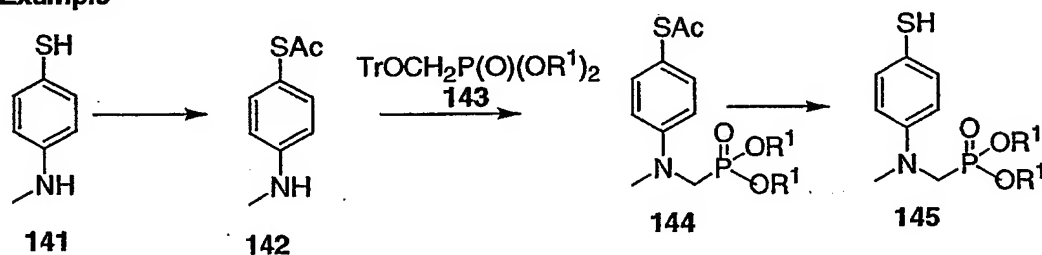


Scheme 24

Method

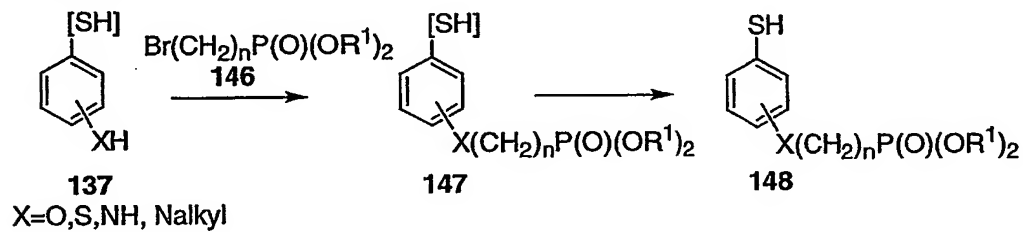


Example

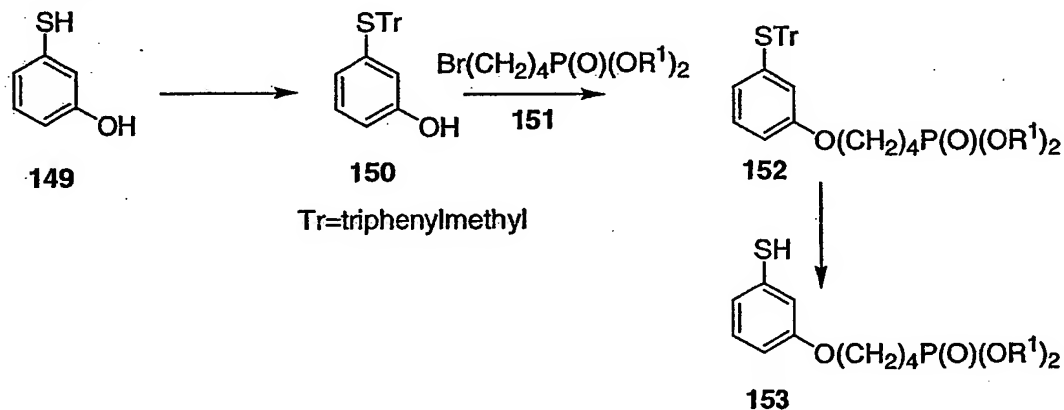


Scheme 25

Method

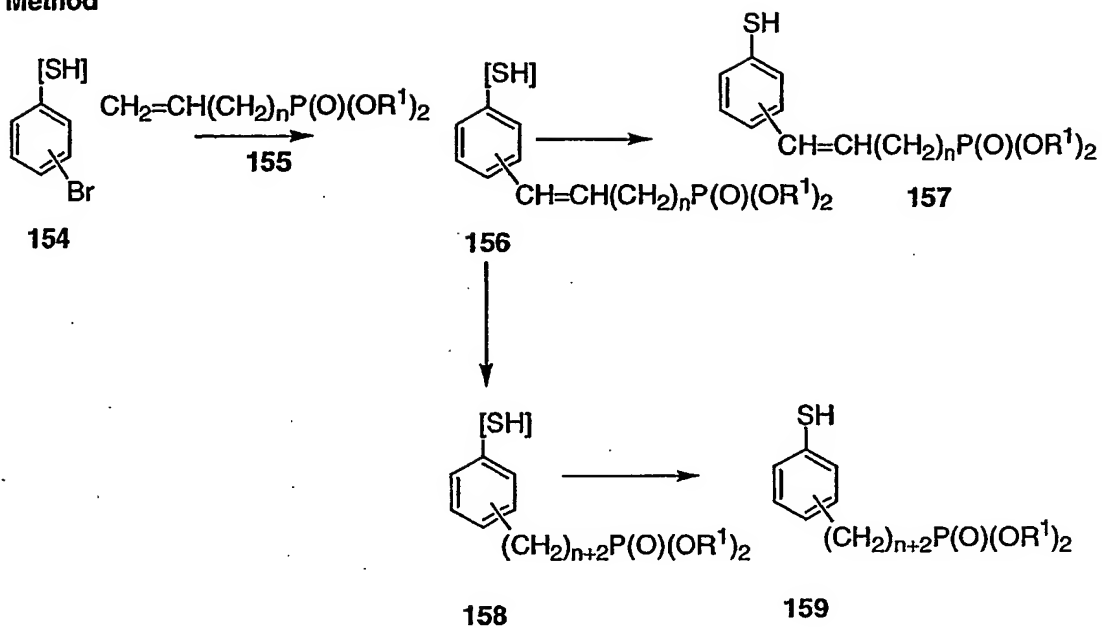


Example

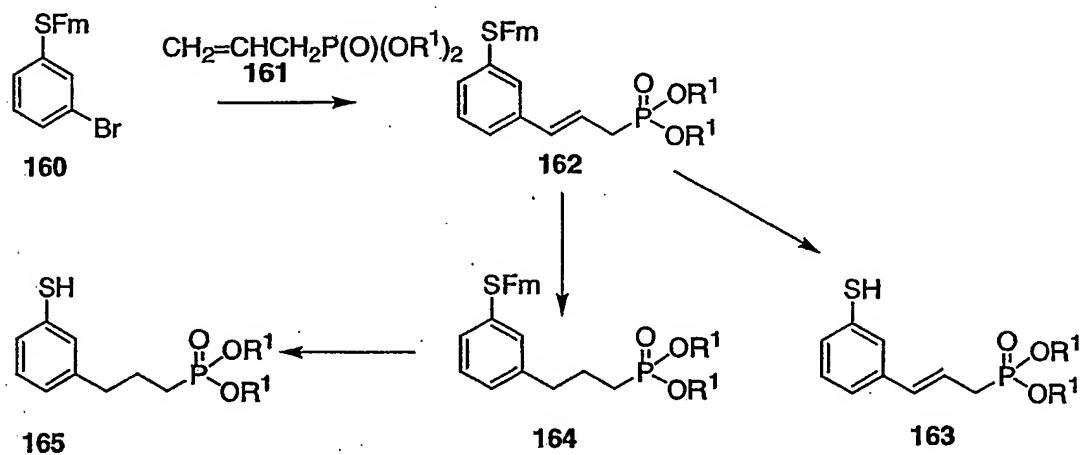


Scheme 26

Method

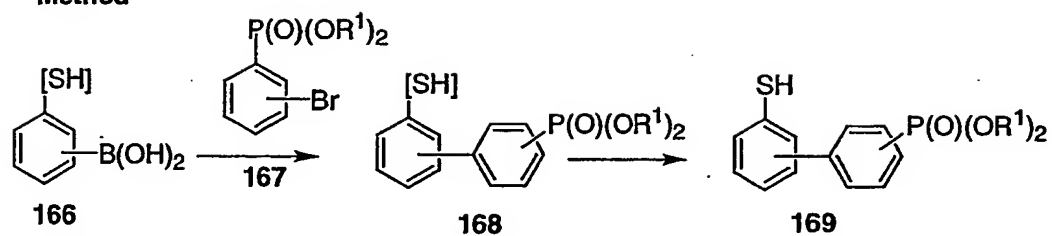


Example

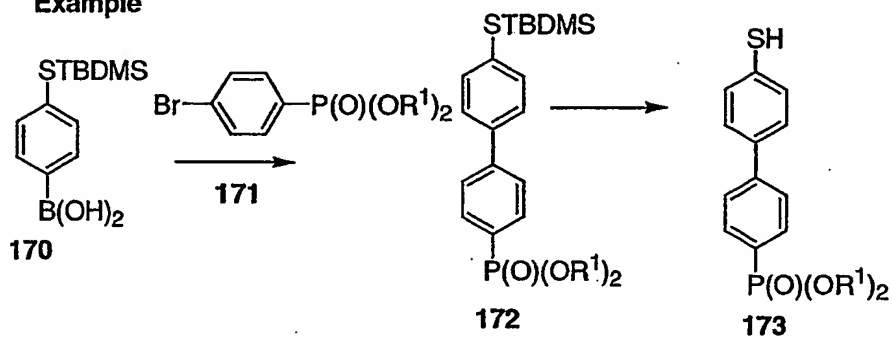


Scheme 28

Method

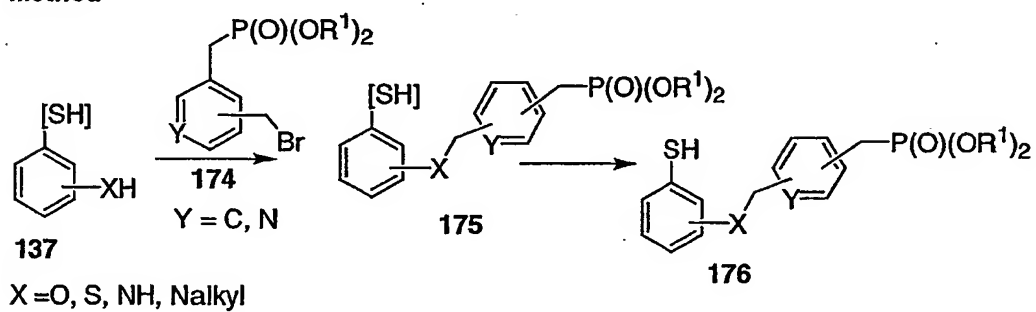


Example

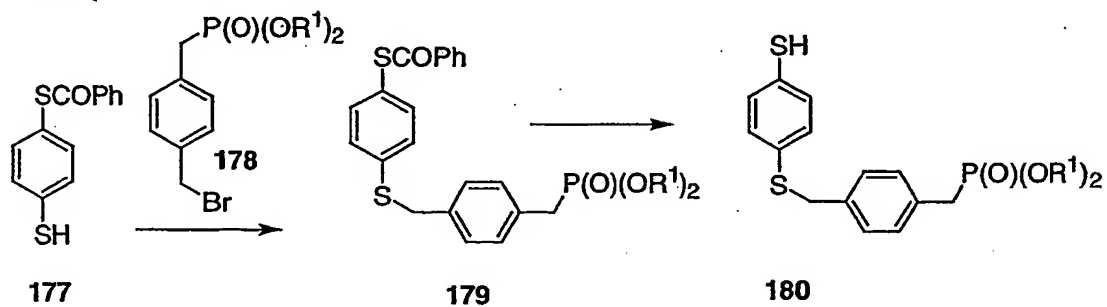


Scheme 29

Method

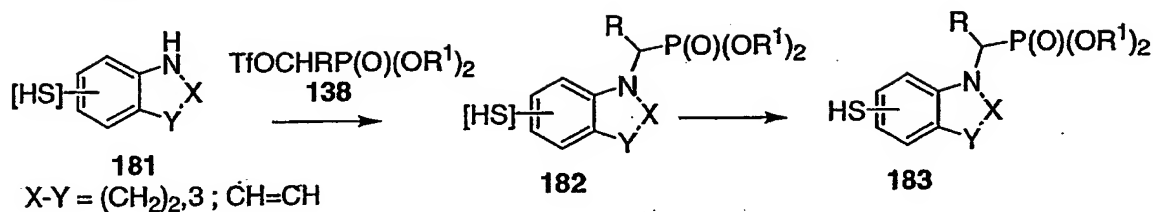


Example

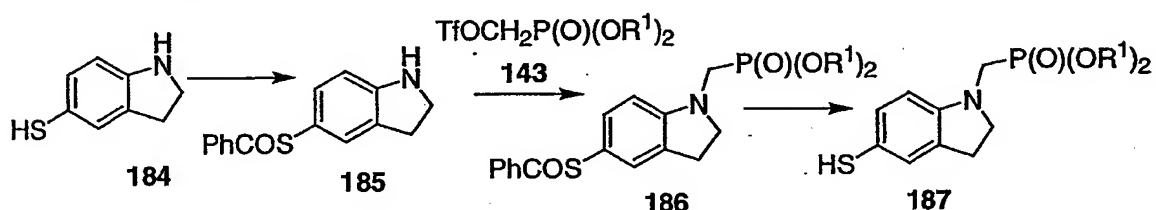


Scheme 30

Method



Example



Preparation of benzoic acid derivatives incorporating phosphonate moieties.

Scheme 31 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid **188** is subjected to halogen-methyl exchange to afford the organometallic intermediate **189**. This compound is reacted with a chlorodialkyl phosphite **115** to yield the phenylphosphonate ester **190**, which upon deprotection affords the carboxylic acid **191**.

10 For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **192**, prepared by bromination of
3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676,
1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The
acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **193**, as described in
Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991,
15 pp. 268, to afford the ester **194**. This compound is treated with boron trifluoride at 0° to
effect rearrangement to the orthoester **195**, known as the OBO ester. This material is treated
with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base
such as imidazole, to yield the silyl ether **196**. Halogen-metal exchange is performed by the
reaction of **196** with butyllithium, and the lithiated intermediate is then coupled with a

chlorodialkyl phosphite 115, to produce the phosphonate 197. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid 198.

- 5 Using the above procedures, but employing, in place of the bromo compound 192, different bromo compounds 188, there are obtained the corresponding products 191.

Scheme 32 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

- 10 In this method, a suitably protected dimethyl hydroxybenzoic acid, 199, is reacted with a brominating agent, so as to effect benzylic bromination. The product 200 is reacted with a sodium dialkyl phosphite, 119, to effect displacement of the benzylic bromide to afford the phosphonate 201.

- For example, 2,5-dimethyl-3-hydroxybenzoic acid, 203, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Second Edition 1990, p. 17, to afford the ether ester 204. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product 204 is then reacted with a brominating agent, for example 20 N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product 205. This compound is then reacted with a sodium dialkyl phosphite 119, using the conditions described above for the preparation of 120, (Scheme 22) to afford the phosphonate 206. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields 25 the carboxylic acid 207.

Using the above procedures, but employing, in place of the methyl compound 203, different methyl compounds 199, there are obtained the corresponding products 202.

- Scheme 33 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids 30 in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid 208 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl

hydroxymethyl phosphonate 134, to afford the coupled product 209, which upon deprotection affords the carboxylic acid 210.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 211, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 212, by
5 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, using the conditions described above for the preparation of 170, to afford the mono-silyl ether 213. This compound is then reacted with a dialkyl hydroxymethylphosphonate 134, under the
10 conditions of the Mitsunobu reaction, as described above for the preparation of 130, (Scheme 23) to afford the coupled product 214. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid 215.

Using the above procedures, but employing, in place of the phenol 211, different phenols or
15 thiophenols 208, there are obtained the corresponding products 210.

Scheme 34 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 216 is coupled, by means of a palladium
20 catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 217. The product 218 can be deprotected to afford the phosphonate 219, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid 220.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 221, prepared as described in
25 WO 9218490, is converted as described above, into the silyl ether OBO ester 222. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 223, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above for the preparation of 156, (Scheme 26) to afford the product 224. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then
30 affords respectively the unsaturated and saturated products 225 and 227.

Using the above procedures, but employing, in place of the bromo compound 221, different bromo compounds 217, and/or different phosphonates 216, there are obtained the corresponding products 219 and 220.

5 Scheme 35 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 217 is converted to the corresponding boronic acid, as described above, (Scheme 28). The product is subjected to a Suzuki coupling reaction, as described above, with a dialkyl bromophenyl
10 phosphonate 229. The product 230 is then deprotected to afford the diaryl phosphonate product 231.

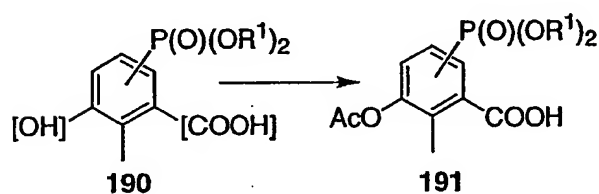
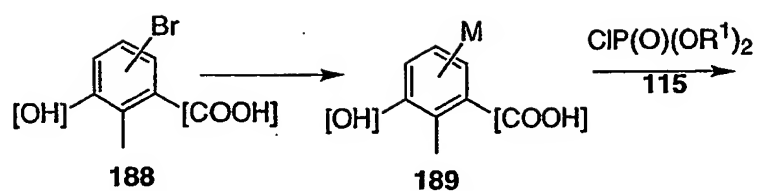
For example, the silylated OBO ester 232, prepared as described above, (Scheme 31), is converted into the boronic acid 233, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate 234, prepared as described in J. Chem. Soc. Perkin
15 Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, as described above for the preparation of 172, (Scheme 28) to afford the diaryl phosphonate 235.

Deprotection, as described above, then affords the benzoic acid 236.

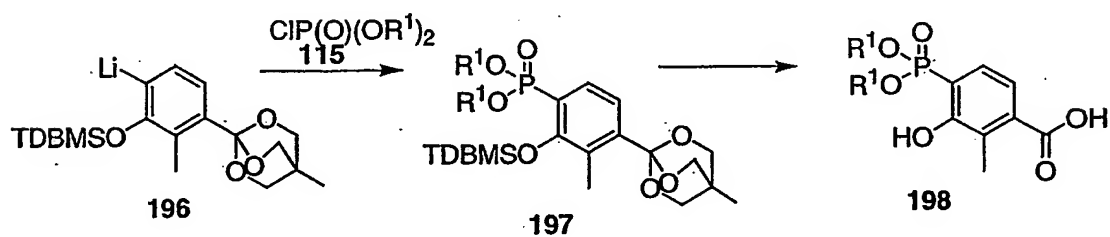
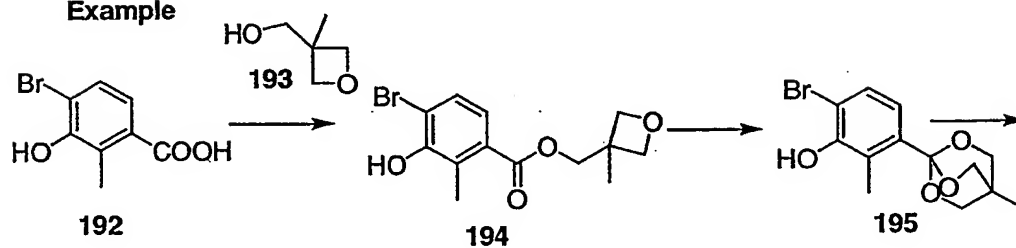
Using the above procedures, but employing, in place of the bromo compound 232, different bromo compounds 217, and/or different phosphonates 229, there are obtained the
20 corresponding carboxylic acid products 231.

Scheme 31

Method

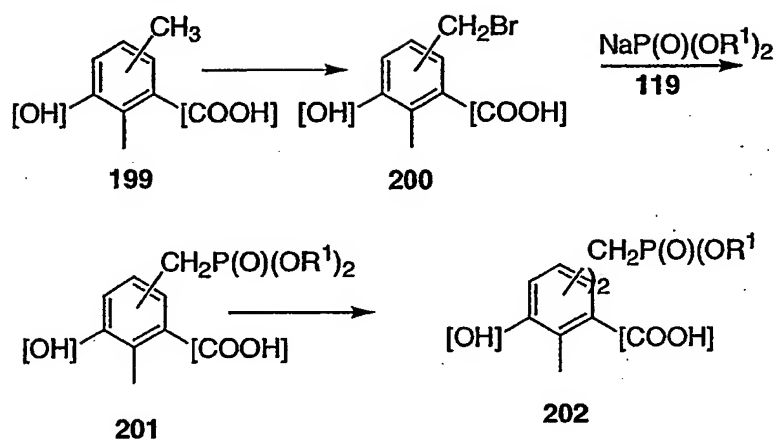


Example

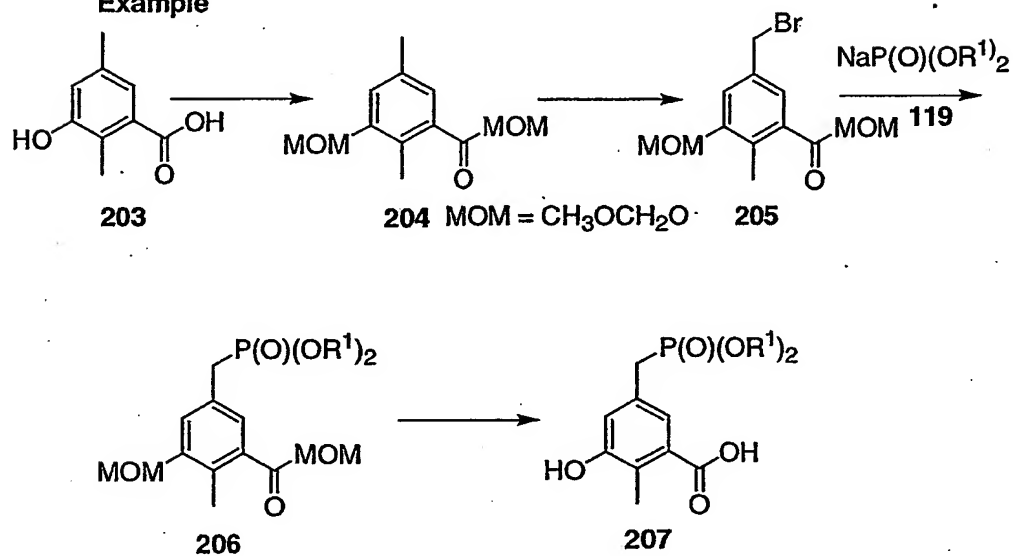


Scheme 32

Method

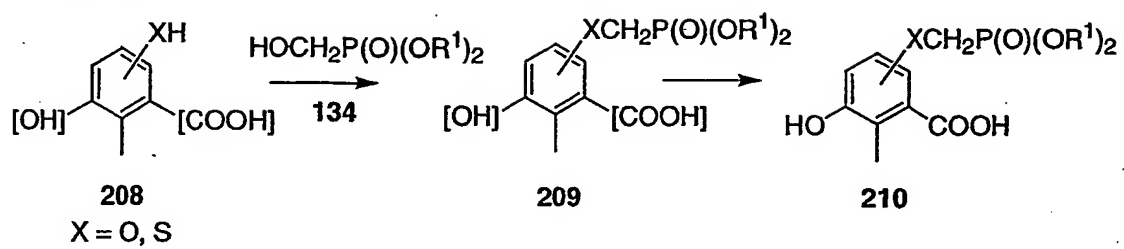


Example

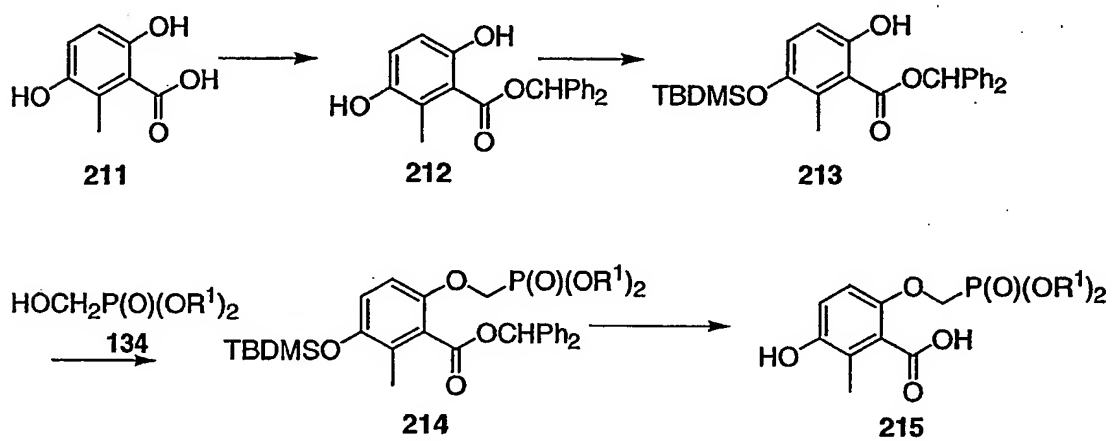


Scheme 33

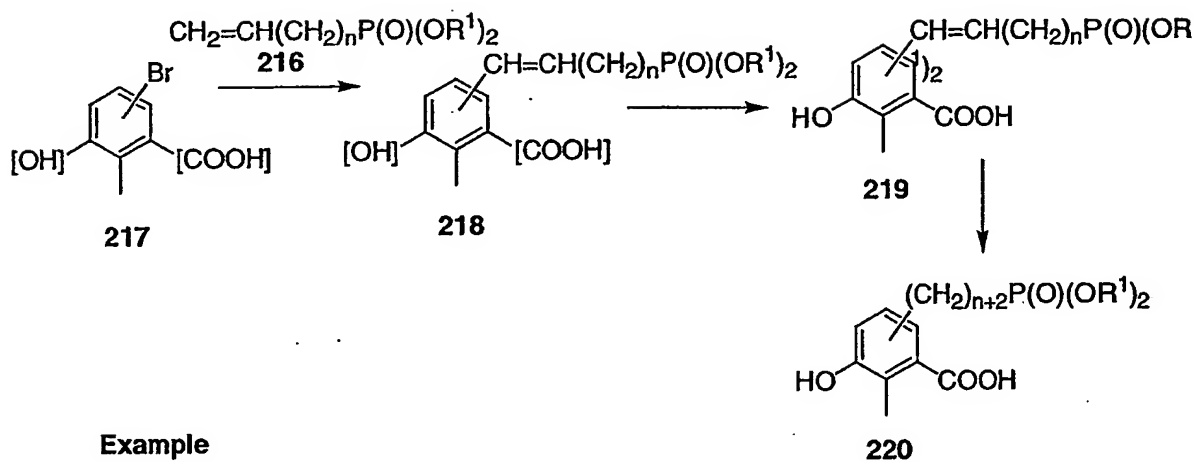
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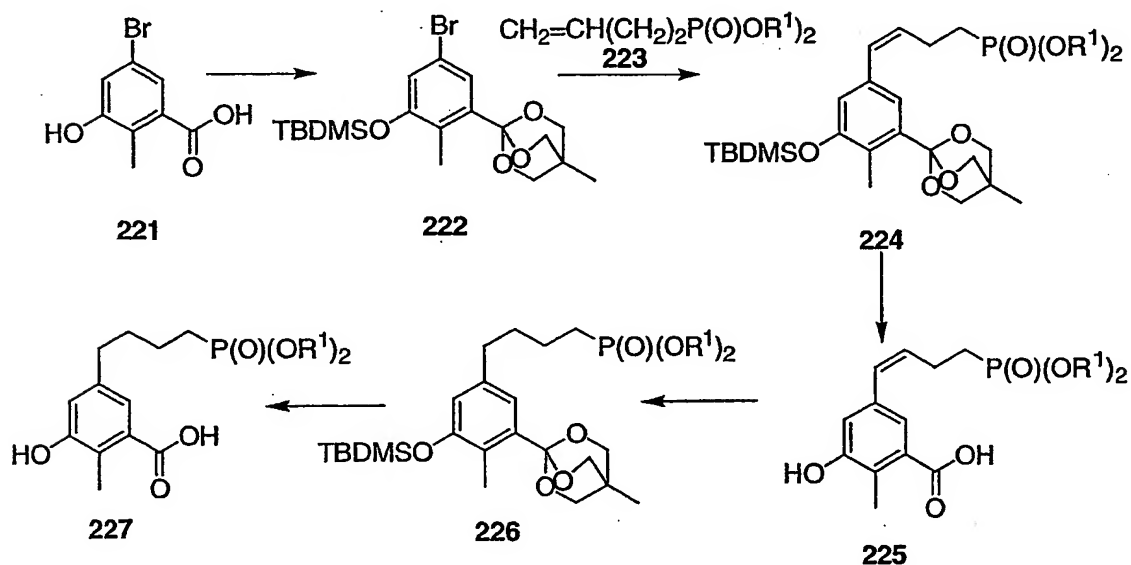
Example



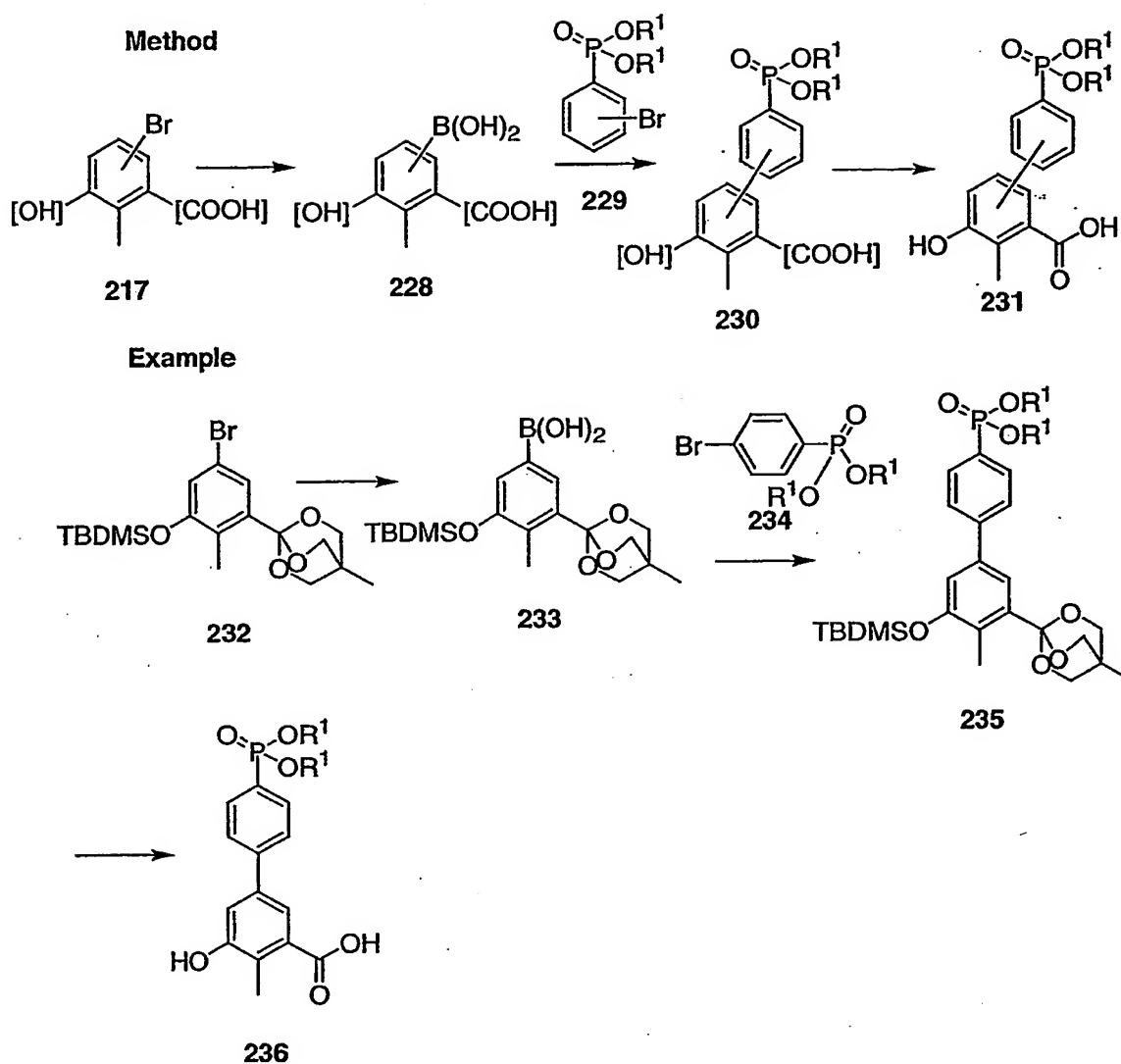
Scheme 34
Method



Example



Scheme 35



Preparation of tert-butylamine derivatives incorporating phosphonate moieties.

- 5 Scheme 36 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethylbromide **237** is reacted with a trialkyl phosphite, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate **238**.

For example, the cbz derivative of 2,2-dimethyl-2-aminoethylbromide **240**, is heated with a trialkyl phosphite at ca 150° to afford the product **241**. Deprotection, as previously described, then affords the free amine **242**.

Using the above procedures, but employing different trisubstituted phosphites, there are
5 obtained the corresponding amines **239**.

Scheme 37 illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain.

An optionally protected alcohol or thiol **243** is reacted with a bromoalkylphosphonate **146**, to
10 afford the displacement product **244**. Deprotection, if needed, then yields the amine **245**.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol **246** is reacted with a dialkyl 4-bromobutyl phosphonate **247**, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and potassium iodide, at ca 60° to afford the phosphonate **248**. Deprotection then affords the free amine **249**.

15 Using the above procedures, but employing different alcohols or thiols **243**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **245**.

Scheme 38 describes the preparation of carbon-linked phosphonate tert butylamine derivatives, in which the carbon chain can be unsaturated or saturated.

20 In the procedure, a terminal acetylenic derivative of tert-butylamine **250** is reacted, under basic conditions, with a dialkyl chlorophosphite **115**, as described above in the preparation of **104**, (Scheme 21). The coupled product **251** is deprotected to afford the amine **252**. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products **253** and **254** respectively.

25 For example, 2-amino-2-methylprop-1-yne **255**, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative **256**, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite
30 **115** to afford the phosphonate **257**. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine **258**. Partial catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for

Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p. 566, produces the olefinic phosphonate **259**, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate **260**.

- 5 Using the above procedures, but employing different acetylenic amines **250**, there are obtained the corresponding products **252**, **253** and **254**.

Scheme 39 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

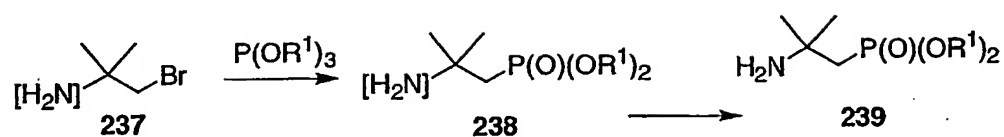
- 10 In this method, an aminoethyl-substituted cyclic amine **261** is reacted with a limited amount of a bromoalkyl phosphonate **146**, using, for example, the conditions described above for the preparation of **147**, (Scheme 25) to afford the displacement product **262**.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine **263**, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with a dialkyl 4-bromobutyl phosphonate

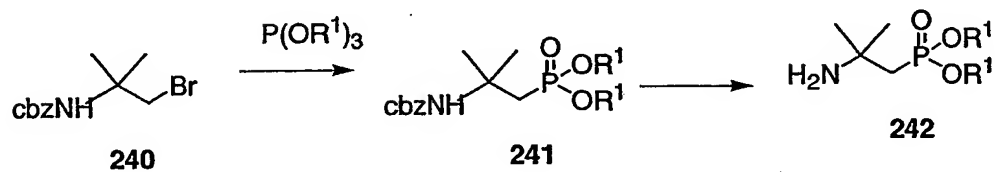
- 15 **151**, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product **264**.
Using the above procedures, but employing different cyclic amines **261**, and/or different bromoalkylphosphonates **146**, there are obtained the corresponding products **262**.

Scheme 36

Method

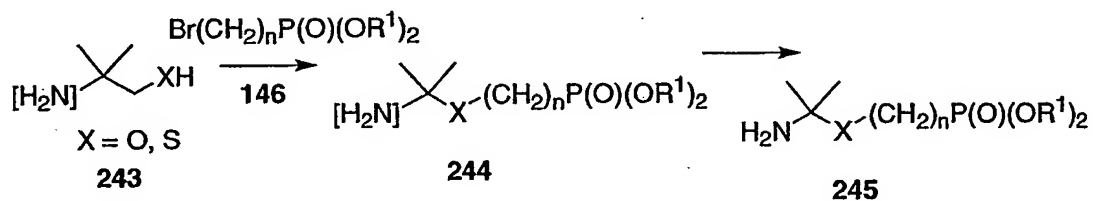


Example

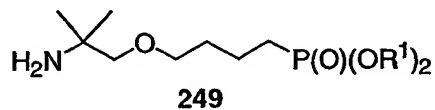
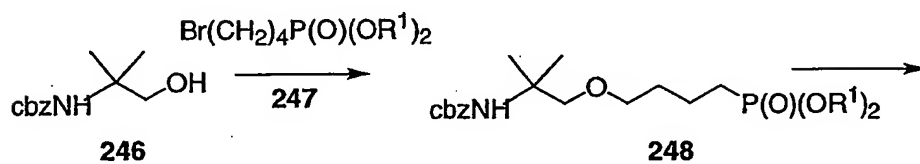


Scheme 37

Method

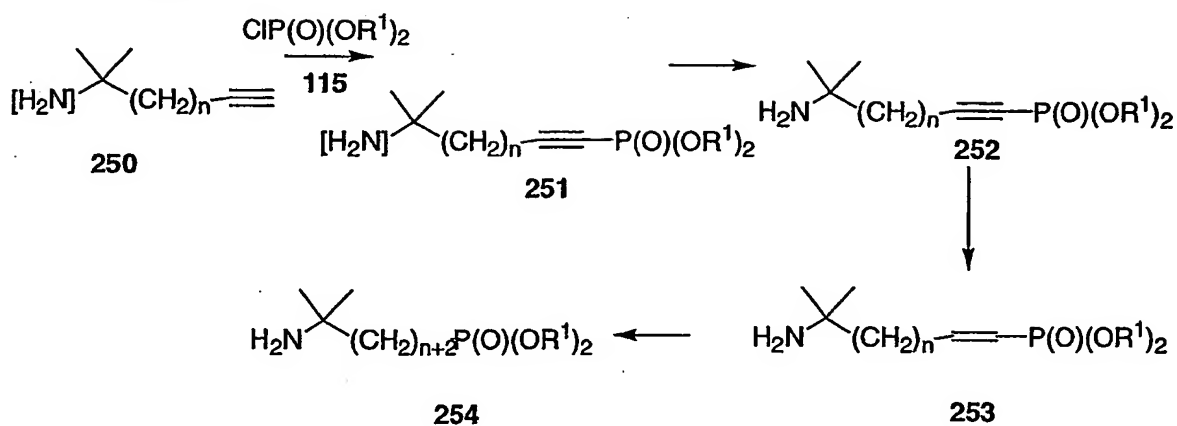


Example

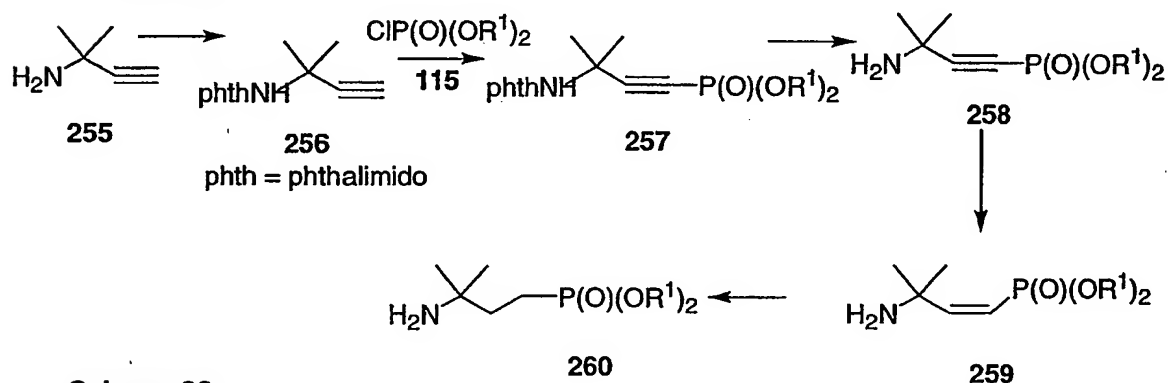


Scheme 38

Method

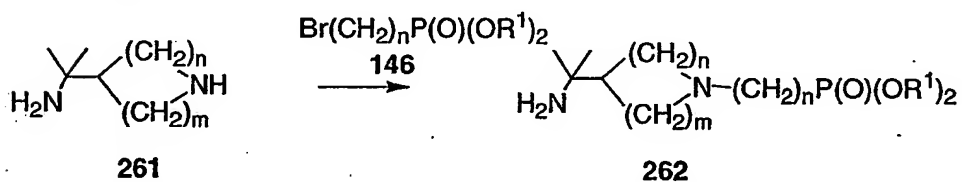


Example

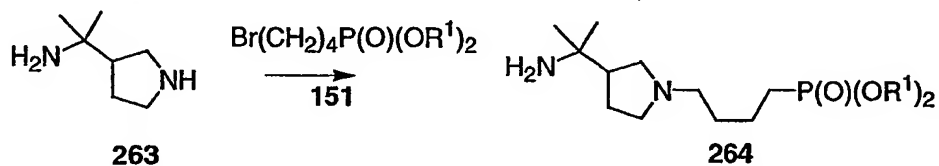


Scheme 39

Method



Example



Preparation of decahydroquinolines with phosphonate moieties at the 6-position.

Chart 6 illustrates methods for the synthesis of intermediates for the preparation of decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the intermediate 265 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 266, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 267. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 267, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 268. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 268 is then treated with acid, for example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 265, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 265 can be obtained from 2-hydroxyphenylalanine 269, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem. Rev., 1995, 95, 1797.

Typically, the substrate 269 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 265, in which R is H.

Catalytic hydrogenation of the latter compound, using, for example, platinum as catalyst, as described in J. Amer. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-substituted decahydroisoquinoline 270. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline 265 is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at ca 50°, to afford the decahydroisoquinoline 270.

Protection of the carboxyl and NH groups present in 270 for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone 276, in which R is trichloroethyl and R₁ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Amer. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl aluminum hydride, as described in J. Amer. Chem. Soc., 80, 5372, 1958, then affords the alcohol 277.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as, for example, isopropanol, at ambient temperature, to afford the alcohol 277. The alcohol 270 carboxyl and NH groups can be protected, for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and by conversion of the NH into the N-cbz group, as described above. The protected alcohol 270 can then be converted into the thiol 271 and the amine 272, by means of displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol 270 can be converted into an activated ester, for example trifluoromethanesulfonyl ester or the methanesulfonate ester 273, by treatment with methanesulfonyl chloride, as described above for the preparation of 63, (Scheme 1). The mesylate 273 is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol 271.

For example, the mesylate 273 is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to afford the thioacetate 274, in which R₂ is COCH₃. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol 271.

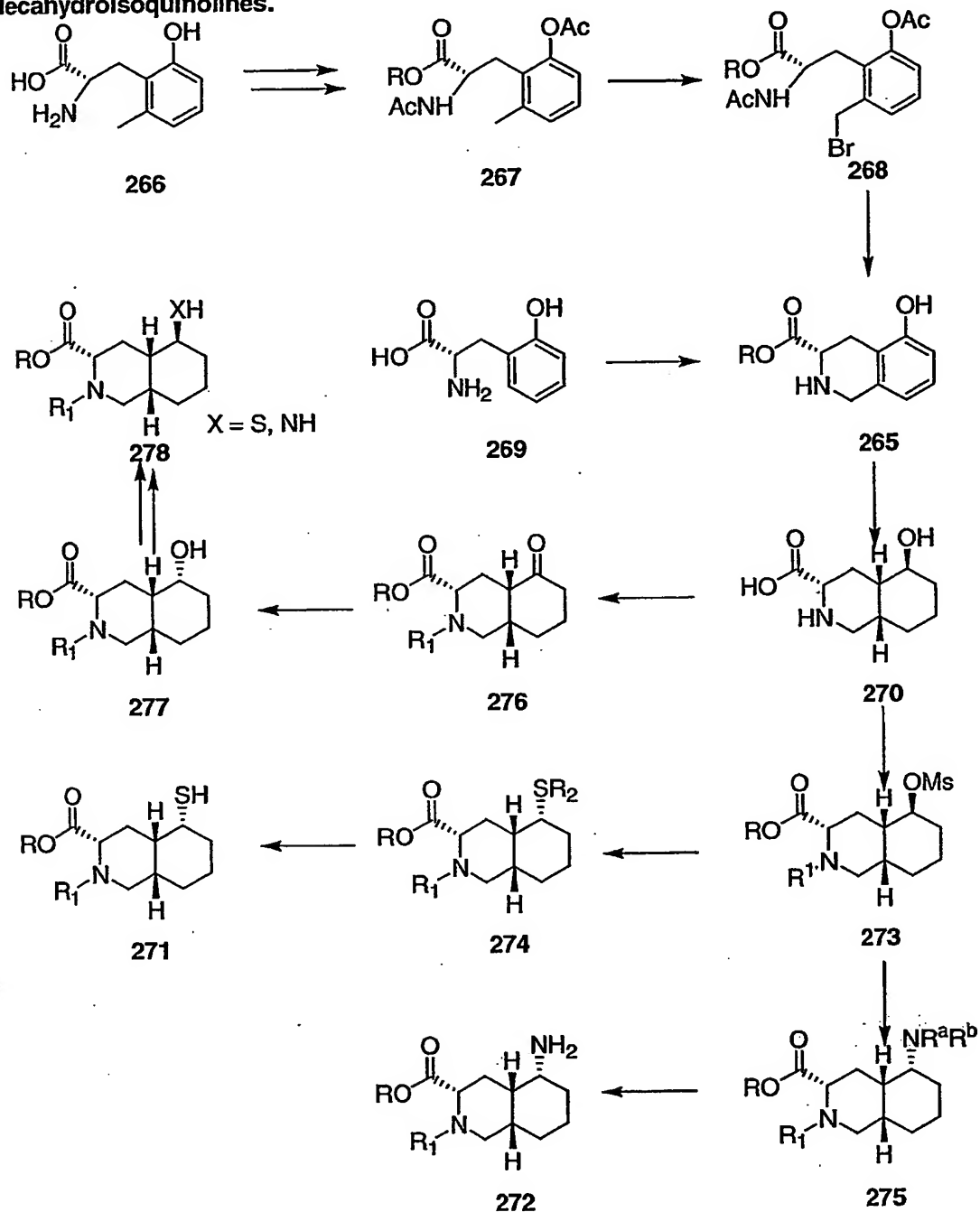
The mesylate 273 can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p. 399, to afford the amine 272.

For example, the mesylate 273 is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product 275, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example
5 by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine 272.

The application of the procedures described above for the conversion of the β -carbinol 270 to the α -thiol 271 and the α -amine 272 can also be applied to the α -carbinol 277, so as to afford the β -thiol and β -amine, 278.

10

Chart 6. Intermediates for the preparation of phosphonate-containing decahydroisoquinolines.



Scheme 40 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain.

In this procedure, an alcohol, thiol or amine 279 is reacted with a bromoalkyl phosphonate

5 146, under the conditions described above for the preparation of 147 (Scheme 25), to afford

the displacement product **280**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **281**.

For example, the compound **282**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **283**, the preparation of which is described in J. Amer. Chem. Soc., 2000, 122, 1554 to afford the displacement product **284**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **285**.

Using the above procedures, but employing, in place of the α -thiol **282**, the alcohols, thiols or amines **270**, **272**, **277**, and **278**, of either α - or β -orientation, there are obtained the corresponding products **281**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 41 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive Organic Transformations, by R. C. Larock, p. 421.

In this procedure, the amines **272** or **278** are reacted with a phosphonate aldehyde **286**, in the presence of a reducing agent, to afford the alkylated amine **287**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **288**.

For example, the protected amino compound **272** is reacted with a dialkyl formylphosphonate **289**, the preparation of which is described in U.S. Patent 3,784,590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate **290**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **291**.

Using the above procedures, but employing, instead of the α -amine **272**, the β isomer, **278** and/or different aldehydes **286**, there are obtained the corresponding products **288**, in which the orientation of the side chain is the same as that of the amine precursor.

Scheme 42 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate 292 is reacted with a mesylate 293, to effect

- 5 displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product 294. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 295. For example, the protected mesylate 273 is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate 296, the preparation of which is described in Aust. J. Chem., 43, 10 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate 297. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 298.
- 15 Using the above procedures, but employing, instead of the phosphonate 296, different phosphonates 292, there are obtained the corresponding products 295.

- Scheme 43 illustrates the preparation of decahydroisoquinoline phosphonates 299 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds 20 are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 300 and a bromomethyl substituted phosphonate 301. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 300. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or 25 lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds 302. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine 299.

- For example, the protected alcohol 303 is reacted at ambient temperature with a dialkyl 3- 30 bromomethyl phenylmethylphosphonate 304, the preparation of which is described above, (Scheme 29). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a

strong base, such as, for example, lithium hexamethyldisylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate **304**, to afford the product **305**. Deprotection of the ester group, followed by conversion of the acid to the tert. butyl amide and N-deprotection, as described below, (Scheme 44) then yields the amine **306**.

5 Using the above procedures, but employing, instead of the β -carbinol **303**, different carbinols, thiols or amines **300**, of either α - or β -orientation, and/or different phosphonates **301**, in place of the phosphonate **304**, there are obtained the corresponding products **299**, in which the orientation of the side-chain is the same as that of the starting material **300**.

10 Schemes 43-43 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 44 illustrates the conversion of the latter group of compounds **307** (in which the group B is link-P(O)(OR¹)₂ and precursor compounds thereto (in which B is an optionally protected precursor to the group link-P(O)(OR¹)₂ such as, for example, OH, SH, NH₂) to the

15 corresponding tert butyl amides **88**.

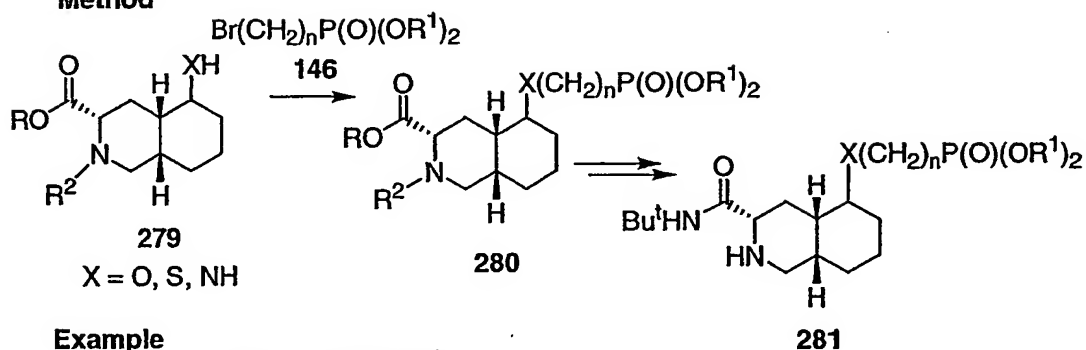
As shown in Scheme 44, the ester compounds **307** are deprotected to form the corresponding carboxylic acids **308**. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is

20 removed by treatment with zinc in acetic acid, as described in J. Amer. Chem. Soc., 88, 852, 1966. Conversion of the carboxylic acid **308** to the tert. butyl amide **309** is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with tert. butylamine, as described above for the preparation of **62** (Scheme 1). Deprotection of the NR² group, as described above, then affords the free amine **88**.

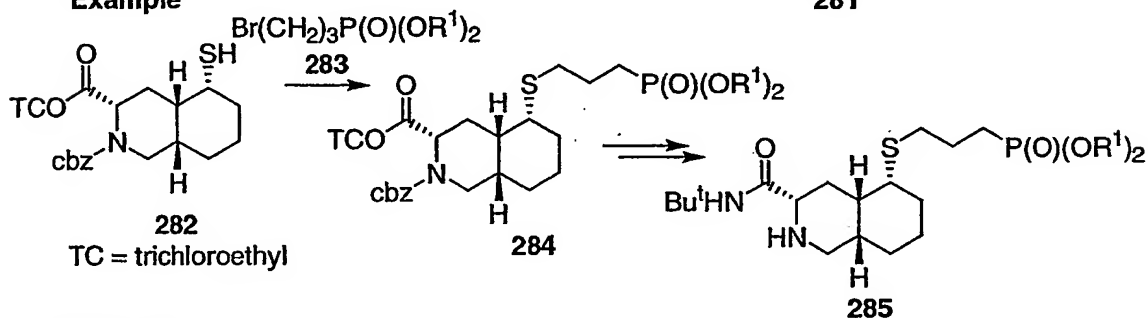
25

Scheme 40

Method

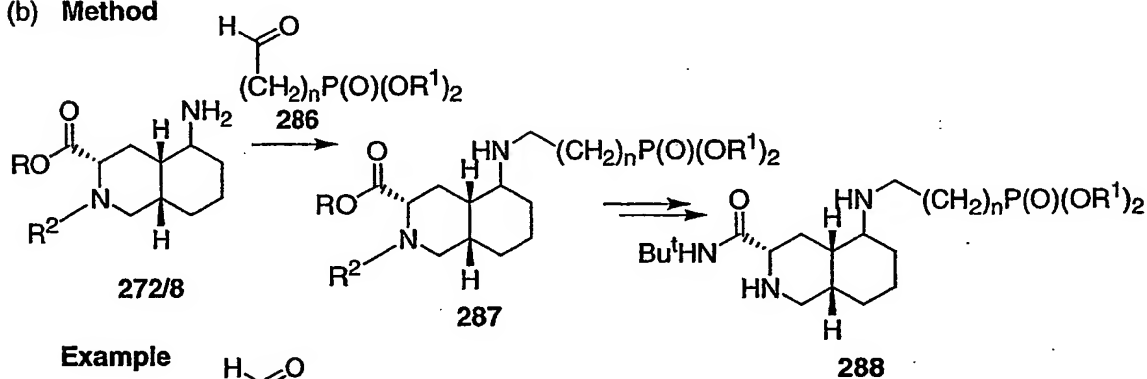


Example

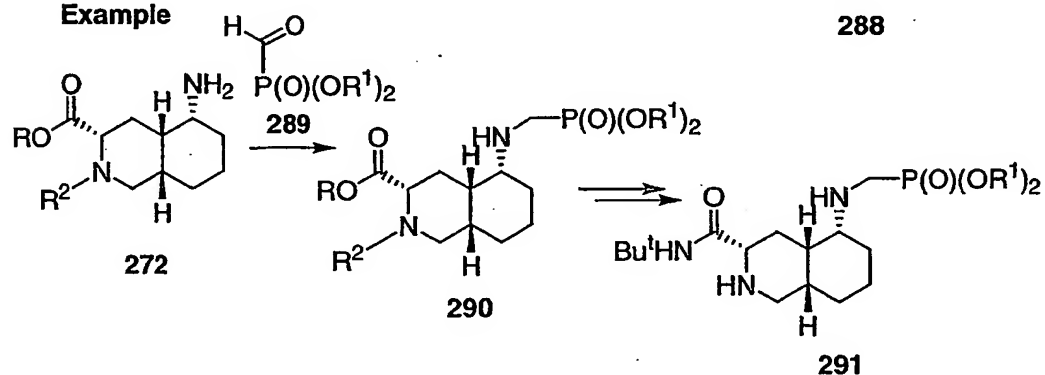


Scheme 41

(b) Method

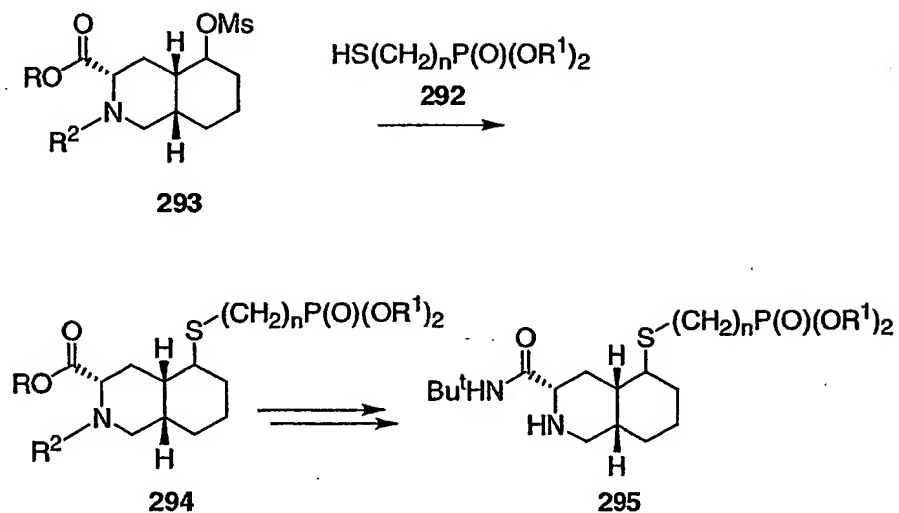


Example

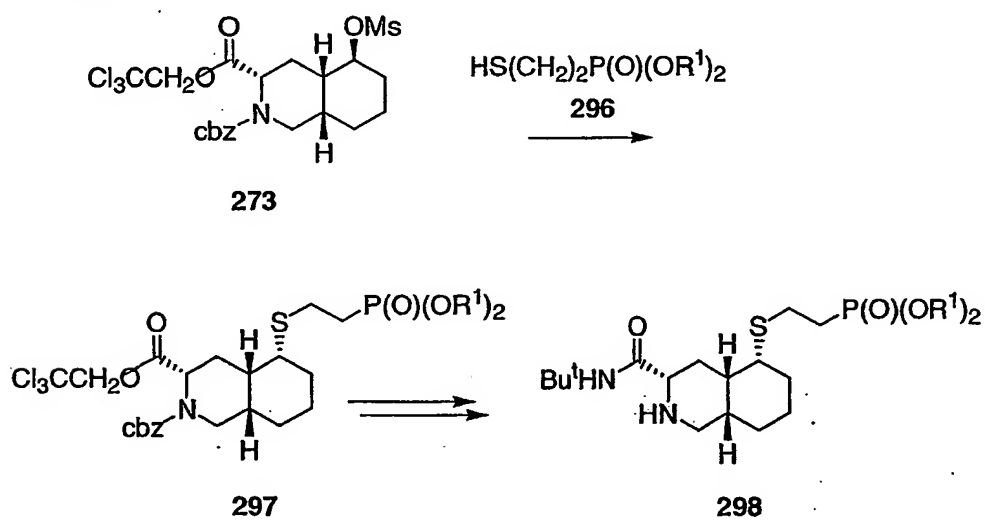


Scheme 42

Method

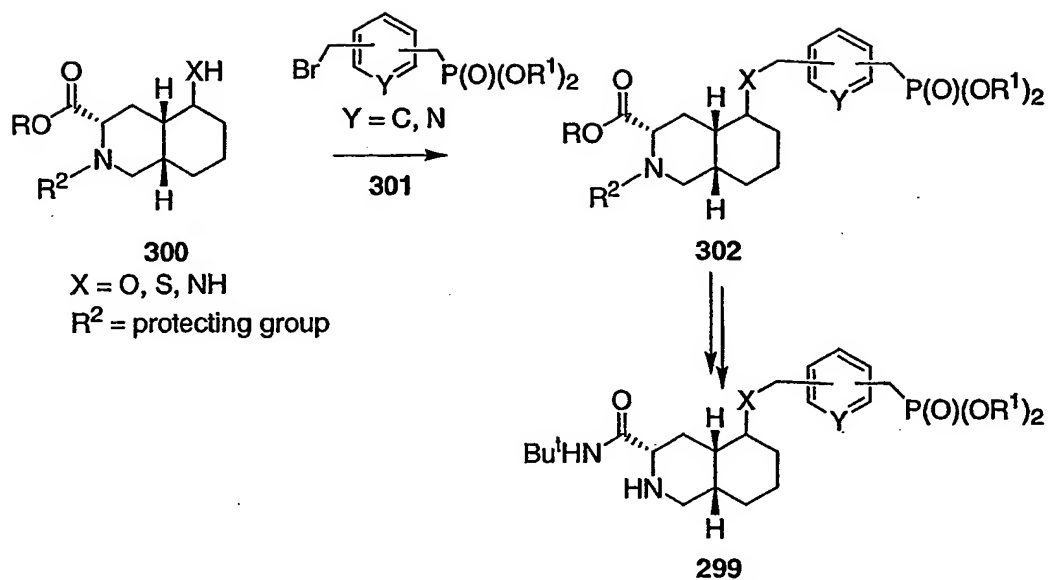


Example

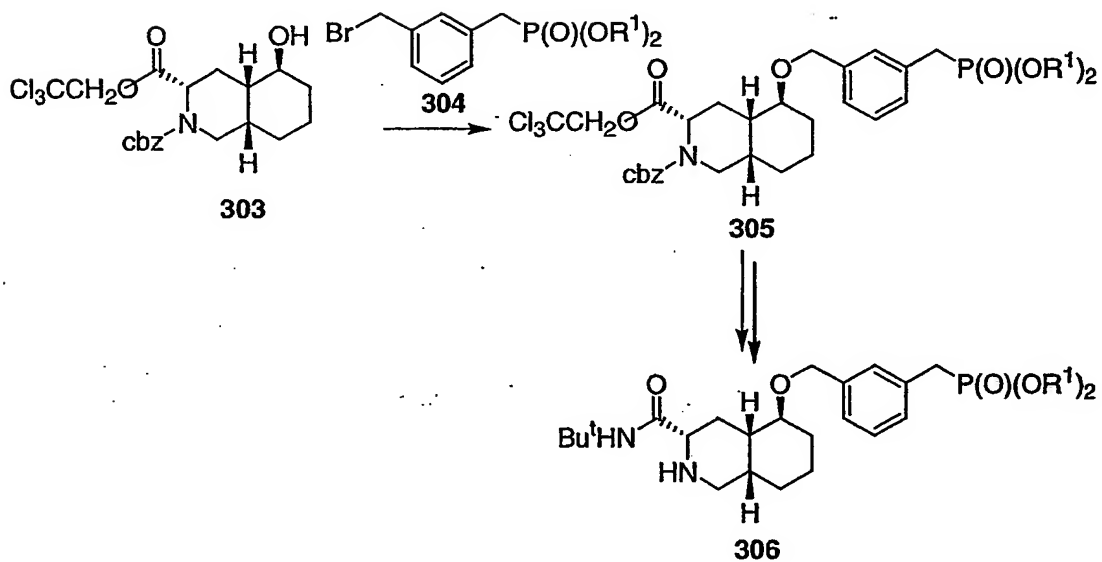


Scheme 43

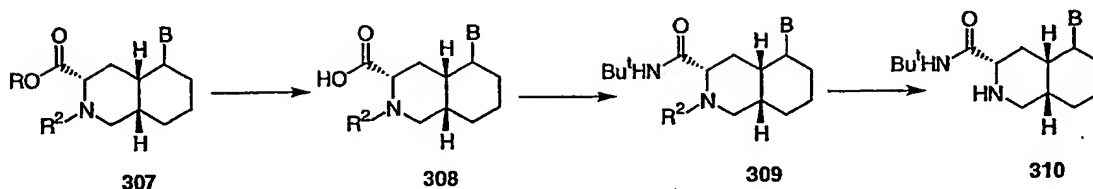
Method



Example



Scheme 44



Preparation of phenylalanine derivatives incorporating phosphonate moieties.

Scheme 45 illustrates the conversion of variously substituted phenylalanine derivatives **311** into epoxides **14a-1**, the incorporation of which into the compounds **2** is depicted in Scheme **14a**.

A number of compounds **311** or **312**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds **311** or **312** are described in the literature. For example, the preparation of compounds **311** or **312** in which X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Amer. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds **311**, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids **312** are protected, for example by conversion to the BOC derivative **313**, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product **313** is then converted into the methyl ester **314**, for example by treatment with ethereal diazomethane. The substituent X in **314** is then transformed, using the methods described below, Schemes 46-48, into the group A. The products **315** are then converted, via the intermediates **316-319**, into the epoxides **14a-1**. The methyl ester **315** is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid **316**. The conversion of the carboxylic acid **316** into the epoxide **14a-1**, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone **317**. The diazoketone is converted into

the chloroketone **318** by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer **319** is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide **14a-1**. Optionally, the above described series of reactions can be performed on the methyl ester **314**, so as to yield the epoxide **14a-1** in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds **314**, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes 46-48.

Scheme 46 depicts the preparation of epoxides **322** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **314** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **320**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH₂OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **321**, which, employing the sequence of reactions shown in Scheme 45, is transformed into the epoxide

322.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **323** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **138**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **324**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **325**.

Using the above procedures, but employing different phenols, thiols, amines and carbinols **314** in place of **323**, and/or different phosphonates **320**, the corresponding products **322** are obtained.

Scheme 47 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 314 is reacted with a dialkyl bromoalkyl phosphonate 146 to afford the product 326. The conditions employed for this reaction are the same as those described above for the preparation of 148, (Scheme 25) The product 326 is then transformed, using the sequence of reactions shown in Scheme 45, into the epoxide 327.

For example, the protected aminoacid 328, prepared as described above (Scheme 45) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate 329, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 330. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide 331.

Using the above procedures, but employing different phenols, thiols, and amines 314 in place of 328, and/or different phosphonates 146, the corresponding products 327 are obtained.

Scheme 48 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

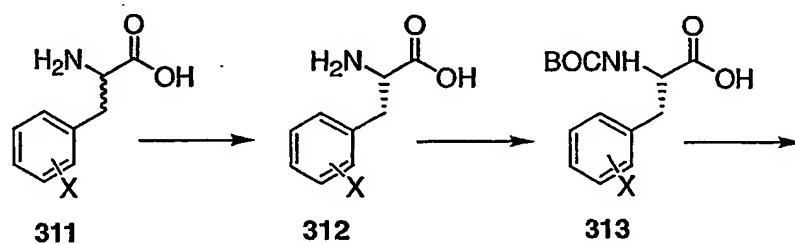
In this procedure, a protected hydroxymethyl-substituted phenylalanine 332 is converted into the halomethyl-substituted compound 333. For example, the carbinol 332 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Amer. Chem. Soc., 108, 1035, 1986 to afford the product 333 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 334. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 335, which, employing the sequence of reactions shown in Scheme 45, is transformed into the epoxide 336.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 337, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative 338, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate 339, the preparation of

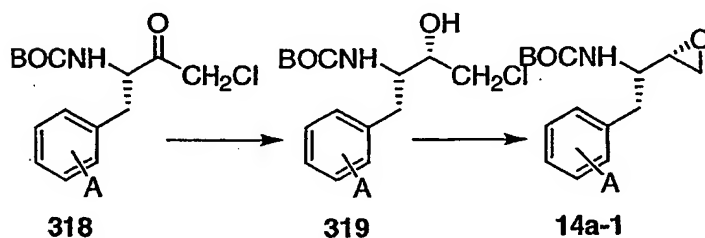
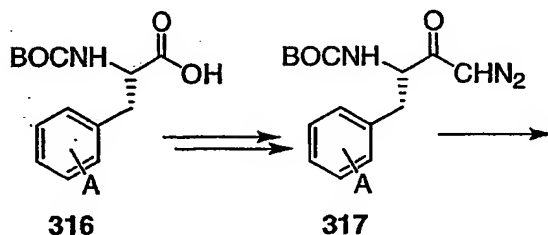
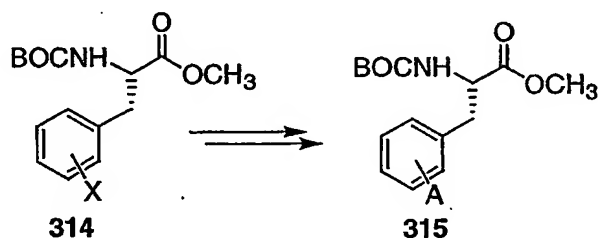
which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **340**. The latter compound is then converted, using the sequence of reactions shown in Scheme 45, into the epoxide **341**.

- 5 Using the above procedures, but employing different carbinols **332** in place of **337**, and/or different phosphonates **334**, the corresponding products **336** are obtained.

Scheme 45

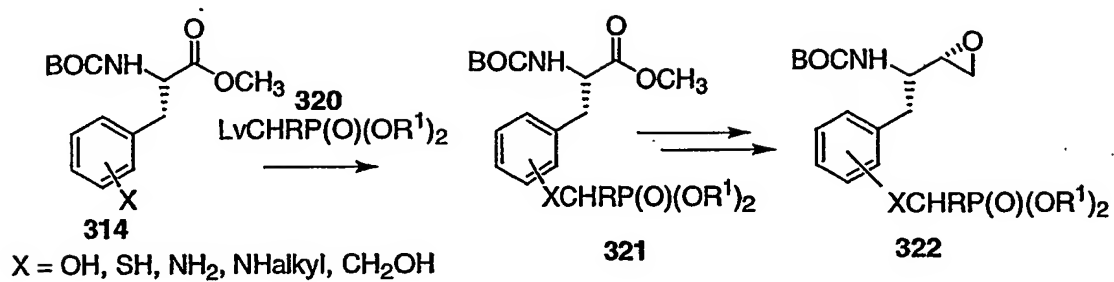


X = OH, SH, NH_2 , NHalkyl, CH_2OH

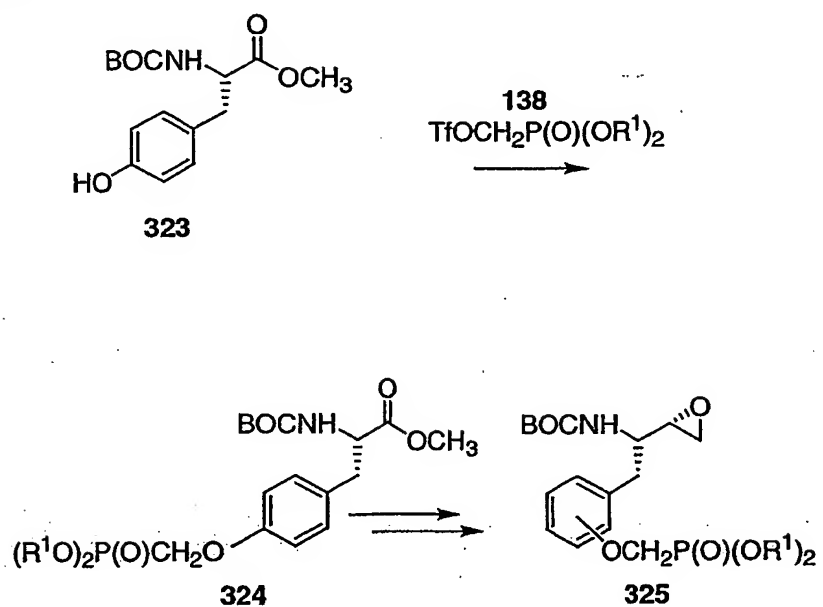


Scheme 46

Method

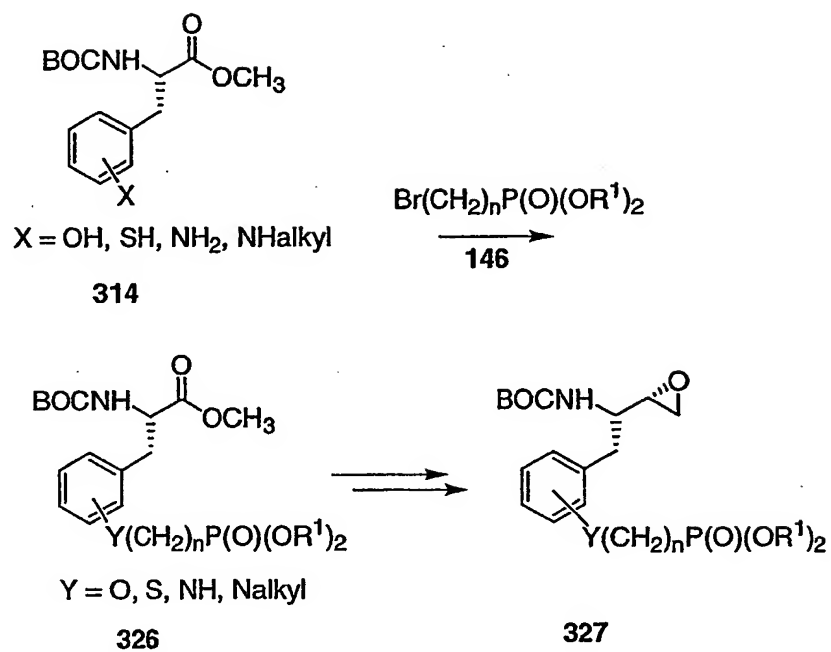


Example

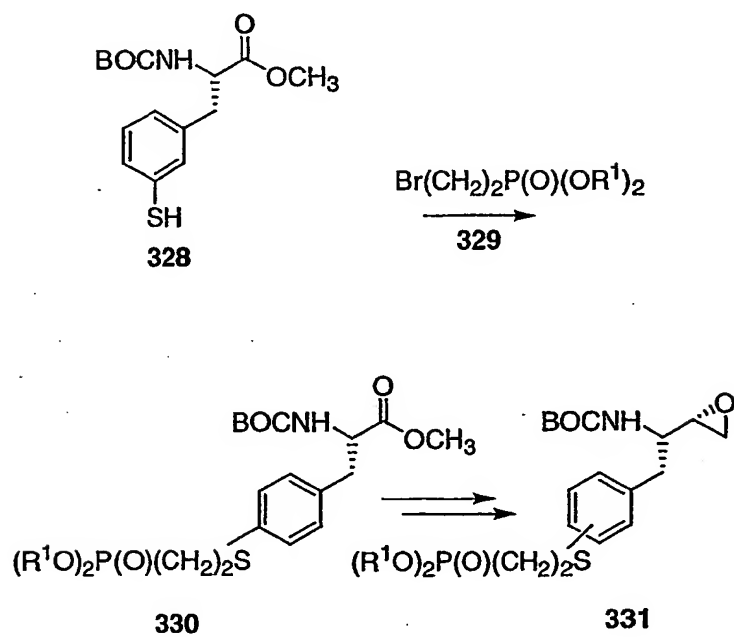


Scheme 47

Method

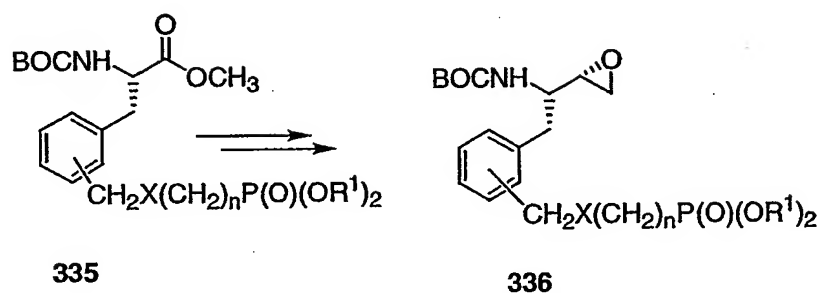
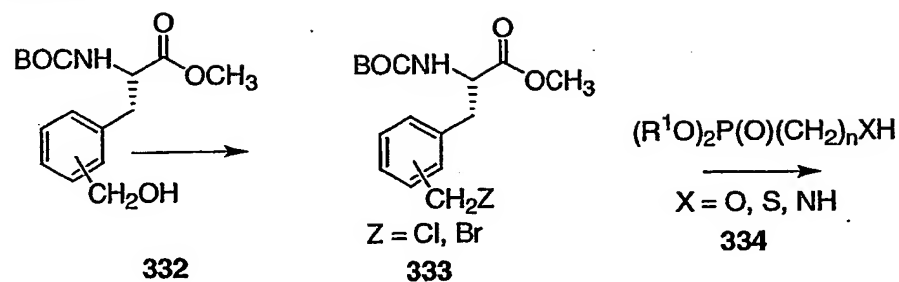


Example

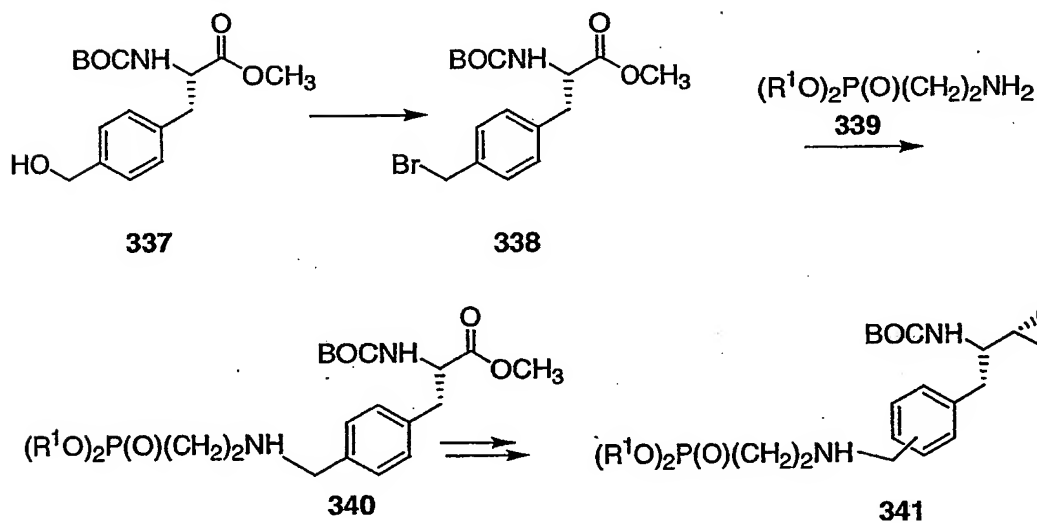


Scheme 48

Method



Example



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1-48 describe the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to phosphonate esters 1-4a, or to precursors thereto,

may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 49. The group R in Scheme 49 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-4a or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-4a. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 342 into the corresponding phosphonate monoester 343 (Scheme 49, Reaction 1) can be accomplished by a number of methods. For example, the ester 342 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 343 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 342 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 343 can be effected by treatment of the ester 342 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 343 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 343 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 343 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 342 or a phosphonate monoester 343 into the corresponding phosphonic acid 344 (Scheme 49, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 343

- in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 344 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 343 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 344 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters 342 in which R¹ is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 342 in which R¹ is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.
- 10 The conversion of a phosphonate monoester 343 into a phosphonate diester 342 (Scheme 49, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 343 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably
15 conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
20 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 342 to the diester 342 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 16). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triaryl phosphine such as triphenyl phosphine. Alternatively, the
25 phosphonate monoester 343 can be transformed into the phosphonate diester 342, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the
30 phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 343 is transformed into the chloro analog RP(O)(OR¹)Cl by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M.

Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP(O)(OR}^1\text{)Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **342**.

- 5 A phosphonic acid R-link-P(O)(OH)_2 can be transformed into a phosphonate monoester $\text{RP(O)(OR}^1\text{)(OH)}$ (Scheme 49, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P(O)(OR}^1\text{)}_2$ **342**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

- 10 A phosphonic acid R-link-P(O)(OH)_2 **344** can be transformed into a phosphonate diester $\text{R-link-P(O)(OR}^1\text{)}_2$ **342** (Scheme 49, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **344** can be transformed into phosphonic esters **342** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **344** can be transformed into phosphonic
15 esters **342** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **342**.

20 **Preparation of carbamates.**

- The phosphonate ester compounds **2-4a** in which the R^5CO group is derived from the carbonic acid derivatives **C38-C49**, the structures of which are shown in Chart 4c, are carbamates. The compounds have the general structure $\text{ROCONHR}'$, wherein the
25 substructure ROCO represents the group R^5CO , as defined in Chart 4c, and the substituent R' represents the substructure to which the amine group is attached. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
30 Scheme 50 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 50, in the general reaction generating carbamates, a carbinol **345** is

converted into the activated derivative 346 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 346 is then reacted with an amine 347, to afford the carbamate product 348. Examples 1 - 7 in Scheme 50 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate
5 alternative methods for the preparation of carbamates.

Scheme 50, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 349. In this procedure, the carbinol 349 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org.
10 Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 350. The latter compound is then reacted with the amine component 347, in the presence of an organic or inorganic base, to afford the carbamate 351. For example, the chloroformyl compound 350 is reacted with the amine 347 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate
15 351. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine..

Scheme 50, Example 2 depicts the reaction of the chloroformate compound 350 with imidazole, 351, to produce the imidazolide 352. The imidazolide product is then reacted with the amine 347 to yield the carbamate 351. The preparation of the imidazolide is performed in
20 an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 50 Example 3, depicts the reaction of the chloroformate 350 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 354. The reaction is conducted
25 in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 363 - 368 shown in Scheme 50, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 363, N-hydroxysuccinimide 364, or pentachlorophenol, 365, the mixed carbonate 354 is obtained by the reaction of the
30 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 366 or 2-hydroxypyridine 367 can be performed in

an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 50 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 352 is employed. In this procedure, a carbinol 349 is reacted with an equimolar amount of carbonyl diimidazole 355 to prepare the intermediate 352. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 352 is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 351.

Scheme 50, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole 357. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 356, to afford the alkoxycarbonyl product 357. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme 50, Example 6 illustrates the preparation of carbamates in which a carbonate $(R''O)_2CO$, 358, is reacted with a carbinol 349 to afford the intermediate alkyloxycarbonyl intermediate 359. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate 351. The procedure in which the reagent 359 is derived from hydroxybenztriazole 363 is described in Synthesis, 1993, 908; the procedure in which the reagent 359 is derived from N-hydroxysuccinimide 364 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 359 is derived from 2-hydroxypyridine 367 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 359 is derived from 4-nitrophenol 368 is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate 358 is conducted in an inert organic solvent at ambient temperature.

Scheme 50, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 360. In this procedure, an alkyl chloroformate 350 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 360. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 351. The reaction is

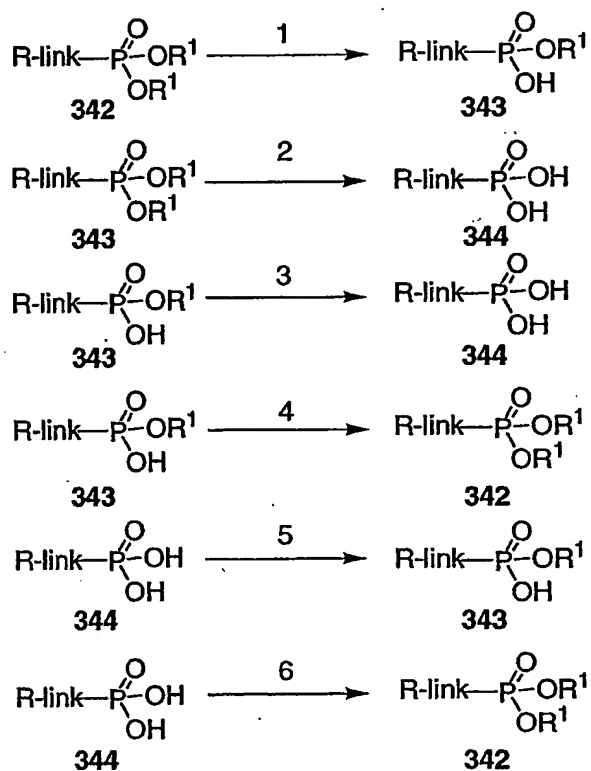
conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 50, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 351.

Scheme 50, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 362. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 351.

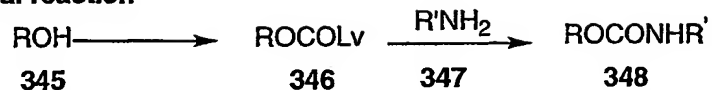
Scheme 50, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 351.

Scheme 49

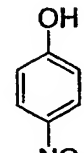
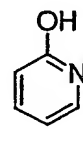
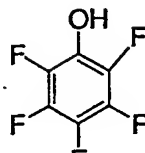
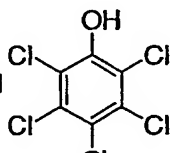
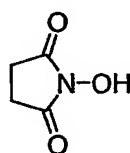
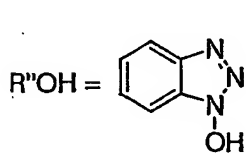
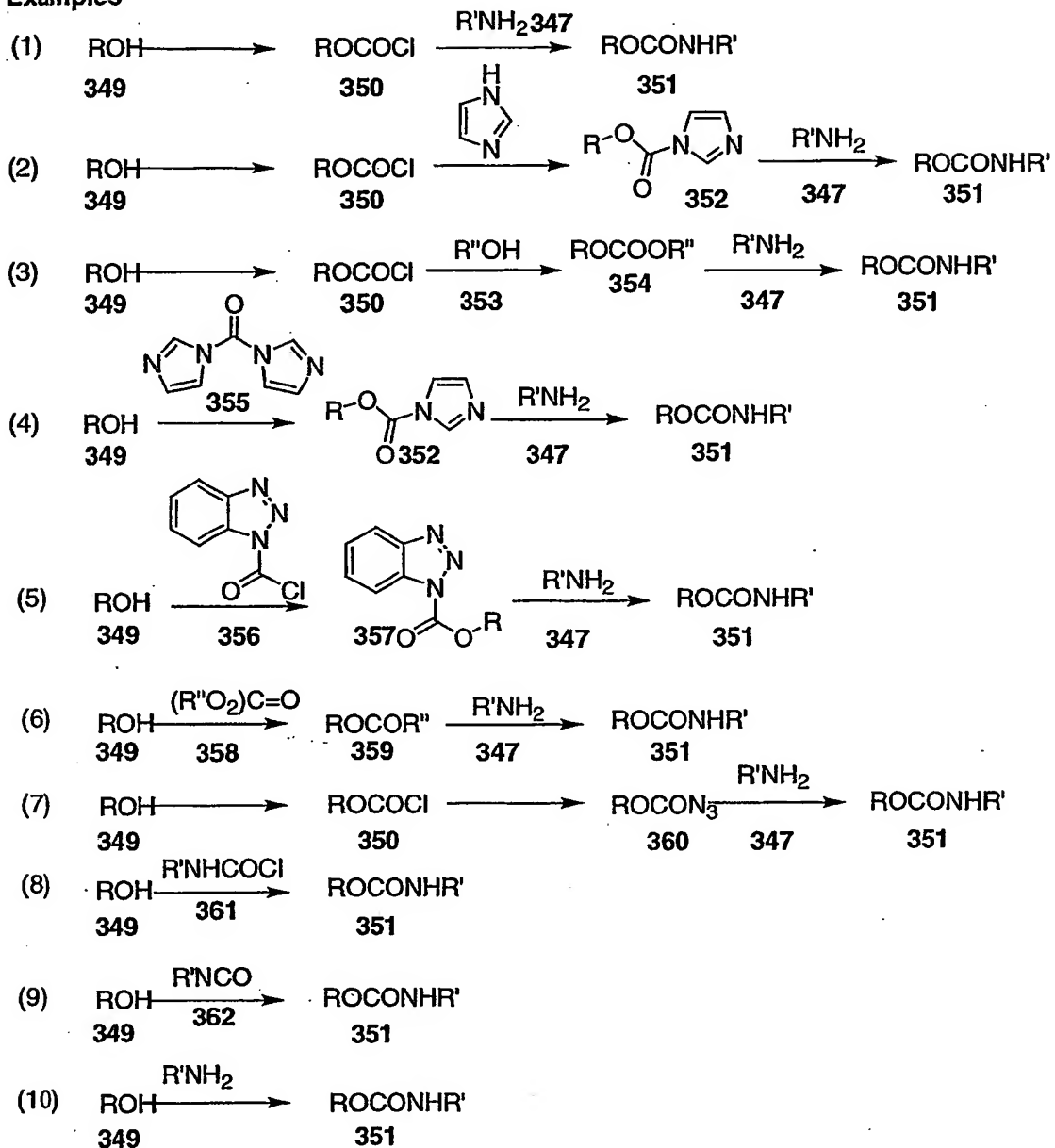


Scheme 50

General reaction



Examples



General applicability of methods for introduction of phosphonate substituents.

The above-described methods for the preparation of phosphonate-substituted thiols, Schemes
5 20 to 30, can, with appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines.

Similarly, preparative methods described above for phosphonate-substituted benzoic acids, tert-butylamines, decahydroisoquinolines and phenylalanines, Schemes 31 to 48, can, with
10 appropriate modifications according to the knowledge of one skilled in the art, be applied to the preparation of phosphonate-substituted thiophenols.

Preparation of compounds 1-4a with phosphonate moieties attached to any substructural component.

15

The chemical transformations described in Schemes 1-50 illustrate the preparation of compounds 1-4 in which the phosphonate ester moiety is attached to the hydroxymethyl benzoic acid group (Schemes 1-3), the phenylthio moiety (Schemes 4-6), the amine moiety (Schemes 7-9), the decahydroisoquinoline moiety (Schemes 10-12) and the phenyl moiety
20 (Schemes 10-14b).

Charts 2 - 4 illustrate various chemical substructures that may be substituted for the phosphonate-containing moieties. For example, in Chart 2, substructures 6, 7 and 8-20e may be substituted for the decahydroisoquinoline moiety, and in Chart 3, substructures 21-26 may be substituted for the group CH_2XR^4 in compounds 1-4. Charts 4a-c illustrate the structures
25 of the compounds R^5COOH which may be incorporated into the phosphonate esters 2-4.

By utilization of the methods described herein for the preparation of, and incorporation of phosphonate-containing moieties, and by the application of the knowledge of one skilled in the art, the phosphonate ester moieties described herein may be incorporated into the amines 6, 7, and 8-20, into the R^4 groups 21-26, and into the carboxylic acids, or functional equivalents thereof, with the structures C1-C49. Subsequently, the thus-obtained phosphonate-ester
30 containing moieties may, utilizing the procedures described above in Schemes 1-14b, be incorporated into the compounds represented by the formula 4a (Chart 1) in which one of the

groups R^2NHCR^3 , R^4 , R^5 or Bu^t contains a phosphonate group of the general formula link-
P(O)(OR¹)₂.

Lopinavir-like phosphonate protease inhibitors (LLPPI)

5

Preparation of the intermediate phosphonate esters.

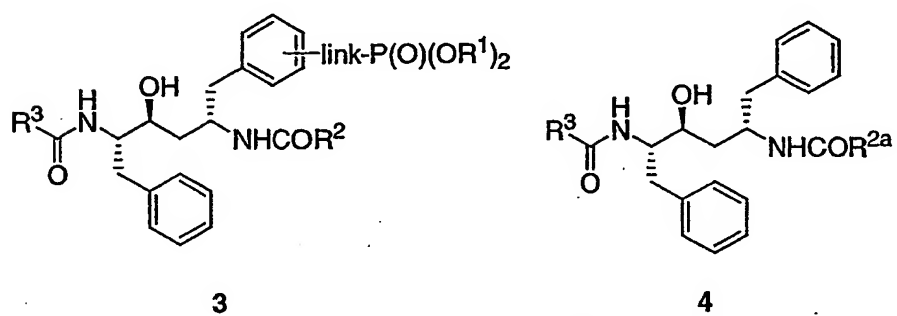
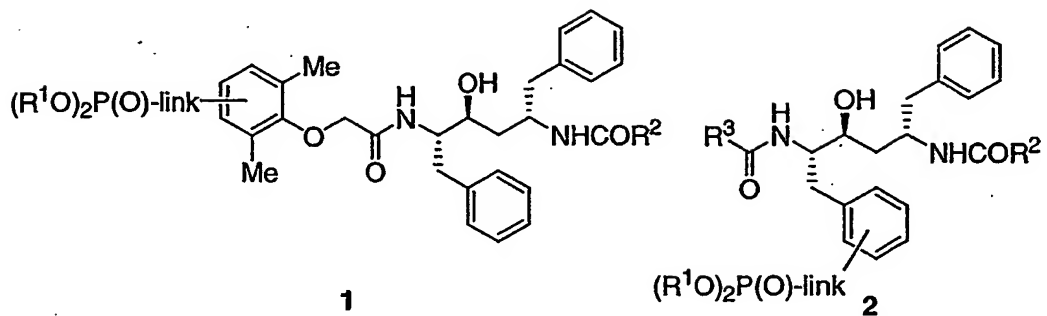
The structures of the intermediate phosphonate esters 1 to 5 and the structures for the component groups R¹ of this invention are shown in Chart 1.

10 The structures of the R²COOH and R³OOH components C1- C49 are shown in Charts 2a, 2b and 2c. Specific stereoisomers of some of the structures are shown in Charts 1, and 2; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 5. Subsequent chemical modifications to the compounds 1 to 5, as described herein, permit the synthesis of the final compounds of this invention.

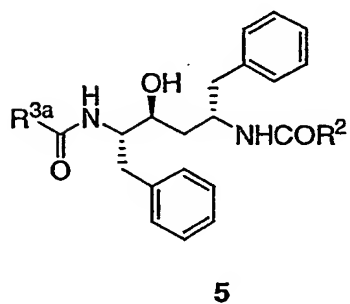
15 The intermediate compounds 1 to 5 incorporate a phosphonate moiety connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 4 and 5 illustrate examples of the linking groups present in the structures 1 – 5, and in which "etc" refers to the scaffold, e.g., lopinavir.

20 Schemes 1 - 33 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 3, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 4 and 5, in which the phosphonate moiety is incorporated into different members of the groups R²COOH and R³COOH, is also described below.

Chart 1 Intermediate phosphonate esters

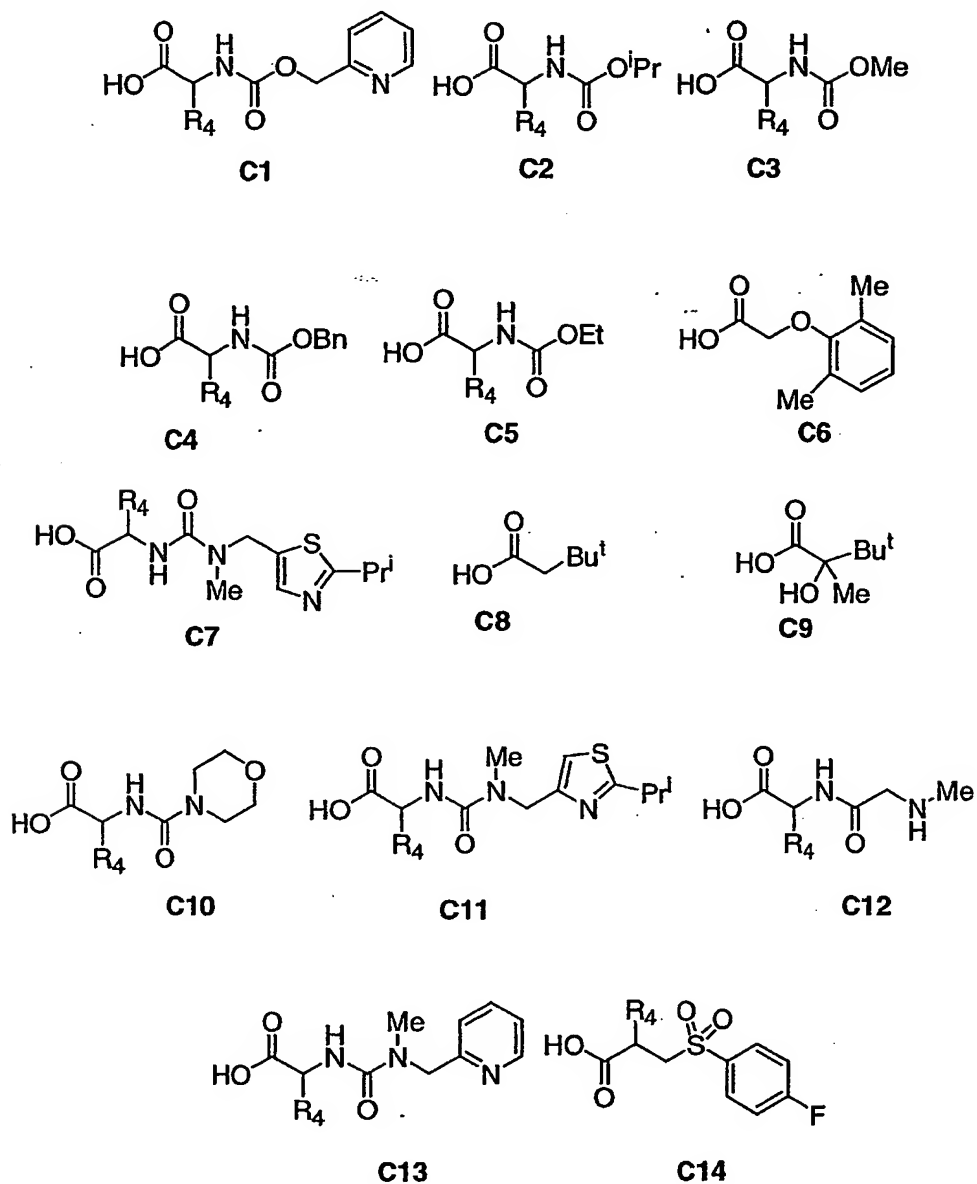


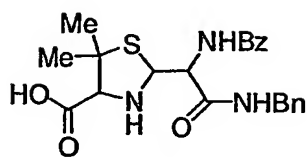
R^{2a} = phosphonate-containing R^2



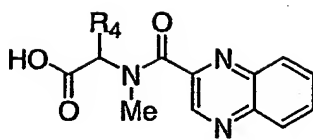
R^{3a} = phosphonate-containing R^3

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

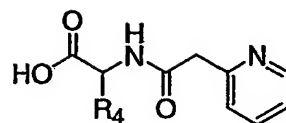
Chart 2a Structures of the R²COOH and R³COOH components



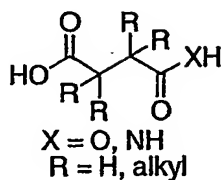
C15



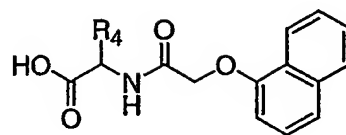
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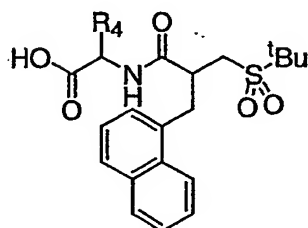
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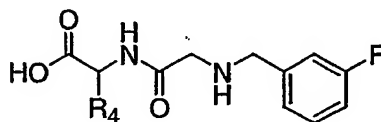
C18



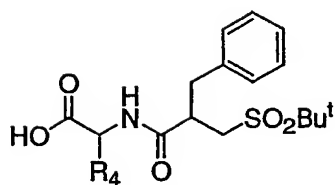
C19



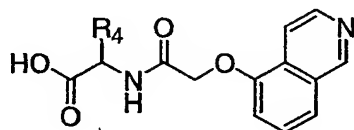
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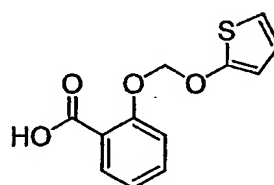
C21



C22

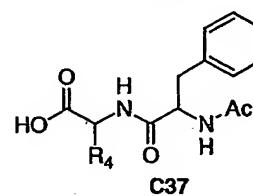
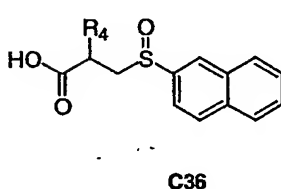
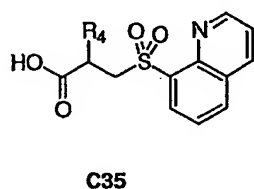
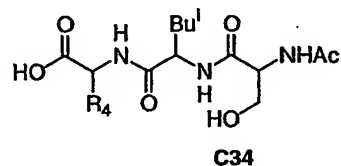
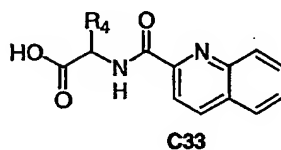
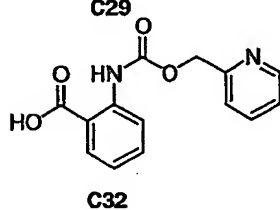
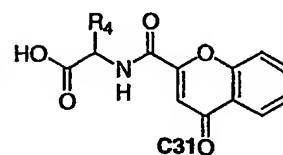
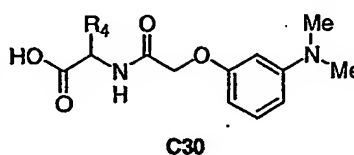
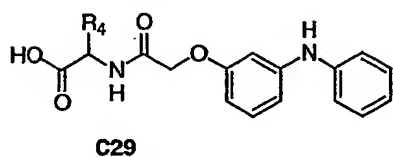
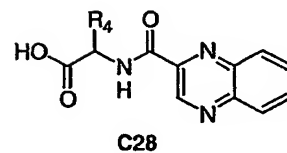
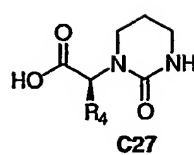
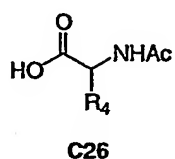
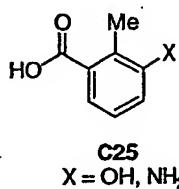


C23



C24

R^4 = alkyl, $\text{CH}_2\text{SO}_2\text{CH}_3$, $\text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $\text{CH}_2\text{NHCOCF}_3$

Chart 2b Structures of the R²COOH and R³COOH components

R⁴ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

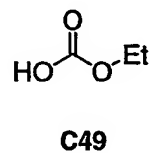
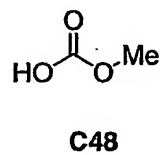
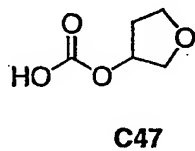
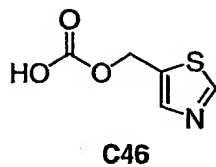
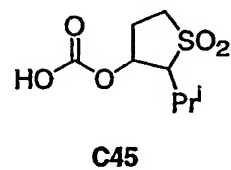
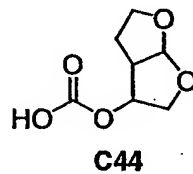
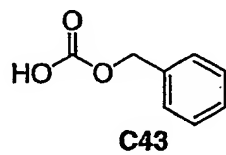
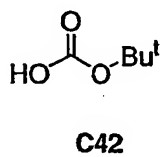
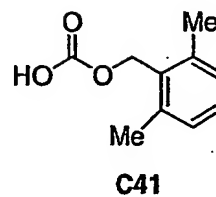
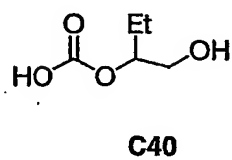
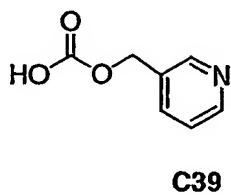
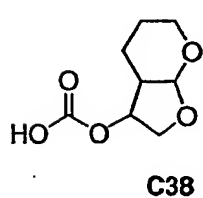
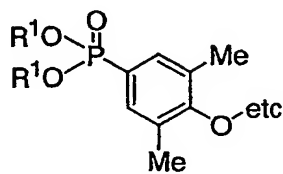
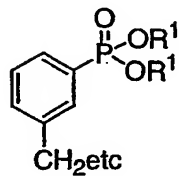
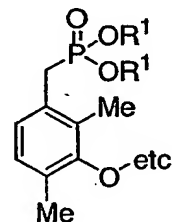
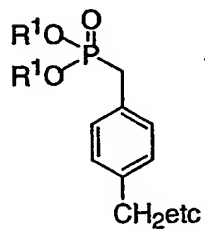
Chart 2c Structures of the R²COOH and R³COOH components

Chart 4 Examples of the linking group between the scaffold and the phosphonate moiety.**link****examples**

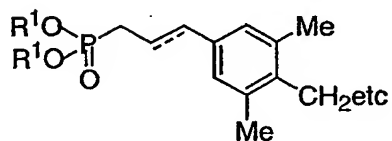
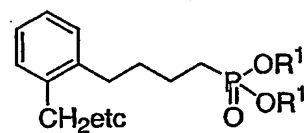
direct bond



single carbon



multiple carbon



hetero atoms

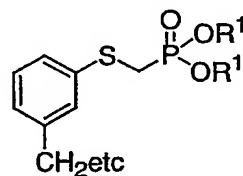
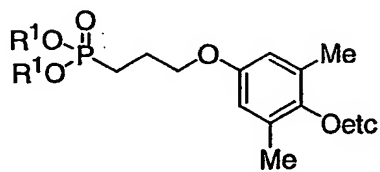
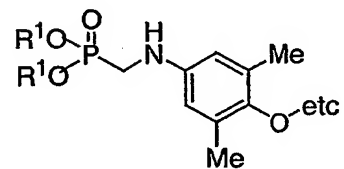
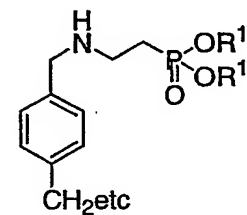
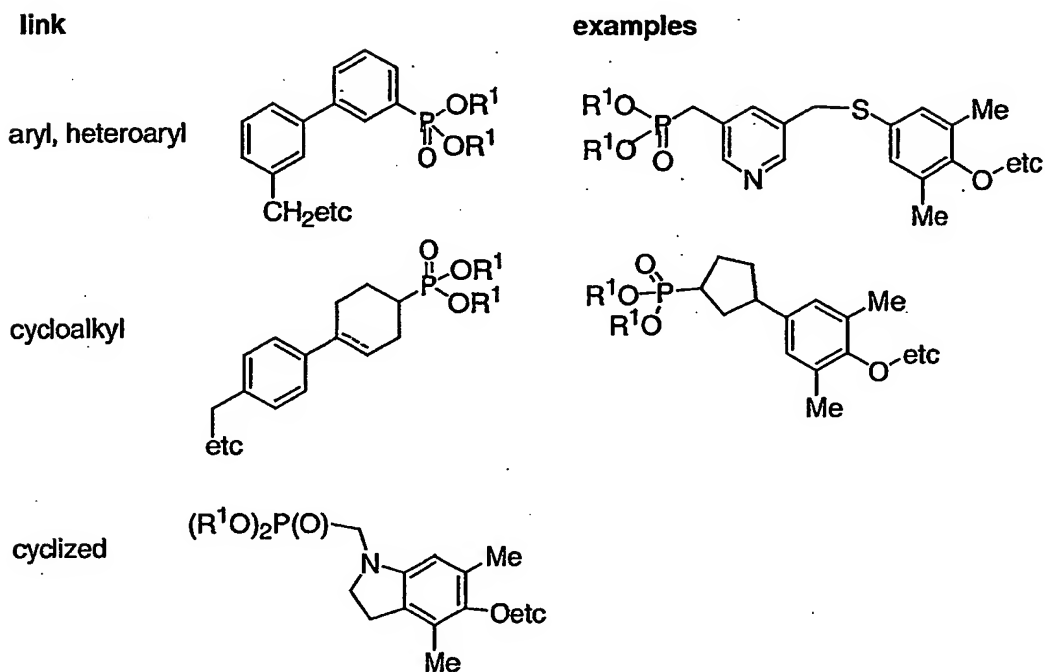


Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.**Protection of reactive substituents.**

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.

10 Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH].

Preparation of the phosphonate intermediates 1.

15

Two methods for the preparation of the phosphonate intermediate compounds 1 are shown in Schemes 1 and 2. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As shown in Scheme 1, 5-amino-2-dibenzylamino-1,6-diphenyl-hexan-3-ol, **1.1**, the preparation of which is described in Org. Process Res. Dev., 1994, 3, 94, is reacted with a carboxylic acid R^2COOH , or an activated derivative **1.2** thereof, to produce the amide **1.3**. The preparation of amides from carboxylic acids and derivatives is described, for example, in
5 Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or
10 dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolid and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

15 The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid is converted into the acid chloride **1.2**, $X = Cl$, and the latter compound is reacted with an equimolar amount of the amine **1.1**, in an aprotic solvent such as,
20 for example, tetrahydrofuran, at ambient temperature. The reaction is conducted in the presence of an organic base such as triethylamine, so as to afford the amide product **1.3**.

The N, N-dibenzylamino amide product **1.3** is then transformed into the free amine compound **1.4** by means of a debenzylation procedure. The deprotection of N-benzyl amines is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and
25 P.G.M Wuts, Wiley, Second Edition 1990, p. 365. The transformation can be effected under reductive conditions, for example by the use of hydrogen or a hydrogen transfer agent, in the presence of a palladium catalyst, or by treatment of the N-benzyl amine with sodium in liquid ammonia, or under oxidative conditions, for example by treatment with 3-chloroperoxybenzoic acid and ferrous chloride.

30 Preferably, the N, N-dibenzyl compound **1.3** is converted into the amine **1.4** by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic

ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for example as described in U.S. Patent 5,914,332.

The thus-obtained amine 1.4 is then transformed into the amide 1.5 by reaction with the carboxylic acid 1.6, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH], [NH], [CHO], Br, as described below. Preparations of the carboxylic acids 1.6 are described below, Schemes 9-14. The amide-forming reaction is conducted under similar conditions to those described above for the preparation of the amide 1.3.

Preferably, the carboxylic acid 1.6 is converted into the acid chloride, and the acid chloride is reacted with the amine 1.4 in a solvent mixture composed of an organic solvent such as ethyl acetate, and water, in the presence of a base such as sodium bicarbonate, for example as described in Org. Process Res. Dev., 2000, 4, 264, to afford the amide product 1.5.

Alternatively, the amide 1.5 can be obtained by the procedure shown in Scheme 2. In this method, 2-tert-butoxycarbonylamino-5-methyl-1,6-diphenyl-hexan-3-ol, 2.1, the preparation of which is described in U.S. Patent 5,4912,53, is reacted with the carboxylic acid 1.6, or an activated derivative thereof, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto. The reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

Preferably, equimolar amounts of the amine 2.1 and the carboxylic acid 1.6 are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide 2.2.

The tert-butoxycarbonyl (BOC) protecting group is then removed from the product 2.2 to afford the free amine 2.3. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate 2.2 with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in U.S. Patent 5,914,332, to afford the free amine product 2.3.

The amine product 2.3 is then reacted with the acid R^2COOH 2.4, or an activated derivative thereof, to produce the amide 2.5. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

Preferably, equimolar amounts of the amine 2.3 and the carboxylic acid 2.4 are reacted in dimethylformamide in the presence of a carbodiimide, such as, for example, 1-dimethylaminopropyl-3-ethylcarbodiimide, as described, for example, in U.S. Patent 5,914,332, to yield the amide 1.5.

The reactions illustrated in Schemes 1 and 2 illustrate the preparation of the compounds 1.5 in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 3 depicts the conversion of the compounds 1.5 in which A is OH, SH, NH, as described below, into the compounds 1 in which A is the group $link-P(O)(OR^1)_2$. In this procedure, the compounds 1.5 are converted, using the procedures described below, Schemes 9-33, into the compounds 1.

Preparation of the phosphonate intermediates 2.

Two methods for the preparation of the phosphonate intermediate compounds 2 are shown in Schemes 4 and 5. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

As depicted in Scheme 4, the tribenzylated phenylalanine derivative 4.1, in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, as described below, is reacted with the anion 4.2 derived from acetonitrile, to afford the ketonitrile 4.3. Preparations of the tribenzylated phenylalanine derivatives 4.1 are described below, Schemes 15-17.

The anion of acetonitrile is prepared by the treatment of acetonitrile with a strong base, such as, for example, lithium hexamethyldisilylazide or sodium hydride, in an inert organic solvent such as tetrahydrofuran or dimethoxyethane, as described, for example, in U.S. Patent 5,491,253. The solution of the acetonitrile anion 4.2, in an aprotic solvent such as tetrahydrofuran, dimethoxyethane and the like, is then added to a solution of the ester 4.1 at low temperature, to afford the coupled product 4.3.

Preferably, a solution of ca. two molar equivalent of acetonitrile, prepared by the addition of ca. two molar equivalent of sodium amide to a solution of acetonitrile in tetrahydrofuran at -40° , is added to a solution of one molar equivalent of the ester 4.1 in tetrahydrofuran at -40° , as described in J. Org. Chem., 1994, 59, 4040, to produce the ketonitrile 4.3.

5 The above-described ketonitrile compound 4.3 is then reacted with an organometallic benzyl reagent, such as a benzyl Grignard reagent or benzyllithium, to afford the ketoenamine 4.5. The reaction is conducted in an inert aprotic organic solvent such as diethyl ether, tetrahydrofuran or the like, at from -80° to ambient temperature, to yield the benzylated product 4.5.

10 Preferably, the ketonitrile 4.3 is reacted with three molar equivalents of benzylmagnesium chloride in tetrahydrofuran at ambient temperature, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 4.5.

The ketoenamine 4.5 is then reduced, in two stages, via the ketoamine 4.6, to produce the
15 amino alcohol 4.7. The transformation of the compound 4.5 to the aminoalcohol 4.7 can be effected in one step, or in two steps, with or without isolation of the intermediate ketoamine 4.6, as described in U.S. Patent 5,491,253.

For example, the ketoenamine 4.5 is reduced with a boron-containing reducing agent such as sodium borohydride, sodium cyanoborohydride and the like, in the presence of an acid such as
20 methanesulfonic acid, as described in J. Org. Chem., 1994, 59, 4040, to afford the ketoamine 4.6. The reaction is performed in an ethereal solvent such as, for example, tetrahydrofuran or methyl tert-butyl ether. The product 4.6 is then reduced with sodium borohydride-trifluoroacetic acid, as described in U.S. Patent 5,491,253, to afford the aminoalcohol 4.7.

Alternatively, the ketoenamine 4.5 can be reduced to the aminoalcohol 4.7 without isolation of
25 the intermediate ketoamine 4.6. In this procedure, as described in U.S. Patent 5,491,253, the ketoenamine 4.5 is reacted with sodium borohydride-methanesulfonic acid, in an ethereal solvent such as dimethoxyethane and the like. The reaction mixture is then treated with a quenching agent such as triethanolamine, and the procedure is continued by the addition of sodium borohydride and a solvent such as dimethylformamide or dimethylacetamide or the
30 like, to afford the aminoalcohol 4.7.

The aminoalcohol 4.7 is converted into the amide 4.8 by reaction with the acid R^2COOH 2.4 or an activated derivative thereof, to produce the amide 4.8. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

The dibenzylated amide product 4.8 is then deprotected to afford the free amine 4.9. The

5 conditions for the debenzylation reaction are the same as those described above for the deprotection of the dibenzyl amine 1.3 to yield the amine 1.4, (Scheme 1).

The amine 4.9 is then reacted with the carboxylic acid R^3COOH (4.10) as defined in Charts 2a -2c, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and

10 1.5.

Alternatively, the amide 4.11 can be prepared by means of the sequence of reactions illustrated in Scheme 5.

In this sequence, the tribenzylated amino acid derivative 4.1 is converted, by means of the reaction sequence shown in Scheme 4, into the dibenzylated amine 4.7. This compound is then
15 converted into a protected derivative, for example the tert-butoxycarbonyl (BOC) derivative 5.1. Methods for the conversion of amines into the BOC derivative are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 327. For example, the amine can be reacted with di-tert-butoxycarbonylanhydride (BOC anhydride) and a base, or with 2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-
20 ON), and the like.

Preferably, the amine 4.7 is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 59143332, to yield the BOC-protected product 5.1.

The N-benzyl protecting groups are then removed from the amide product 5.1 to afford the
25 free amine 5.2. The conditions for this transformation are similar to those described above for the preparation of the amine 1.4, (Scheme 1).

Preferably, the N, N-dibenzyl compound 5.1 is converted into the amine 5.2 by means of hydrogen transfer catalytic hydrogenolysis, for example by treatment with methanolic ammonium formate and 5% palladium on carbon catalyst, at ca. 75° for ca. 6 hours, for
30 example as described in US Patent 5914332

The amine compound 5.2 is then reacted with the carboxylic acid R^3COOH , or an activated derivative thereof, to produce the amide 5.3. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5, (Scheme 1).

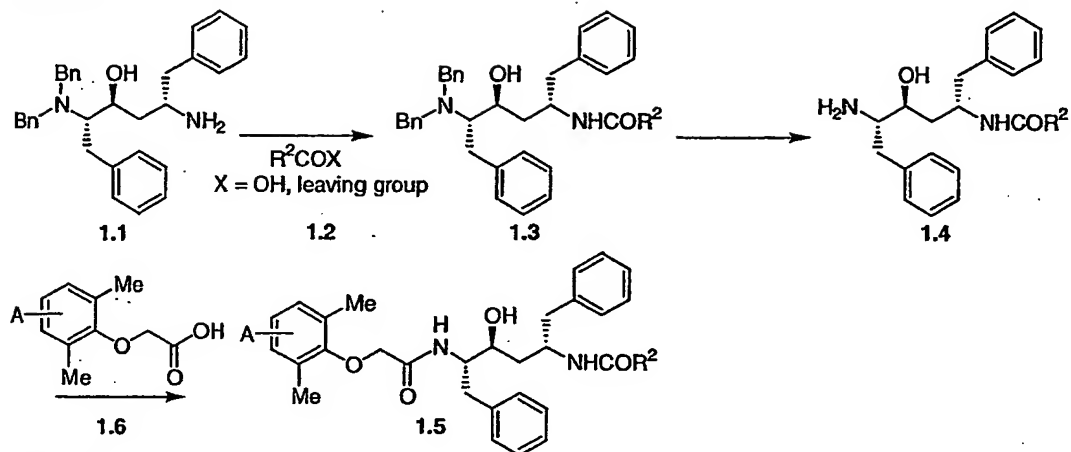
The BOC-protected amide 5.3 is then converted into the amine 5.4 by removal of the BOC protecting group. The conditions for this transformation are similar to those described above for the preparation of the amine 2.3 (Scheme 2). The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride.

Preferably, the BOC group is removed by treatment of the substrate 5.3 with trifluoroacetic acid in dichloromethane at ambient temperature, for example as described in US Patent 5914232, to afford the free amine product 5.4.

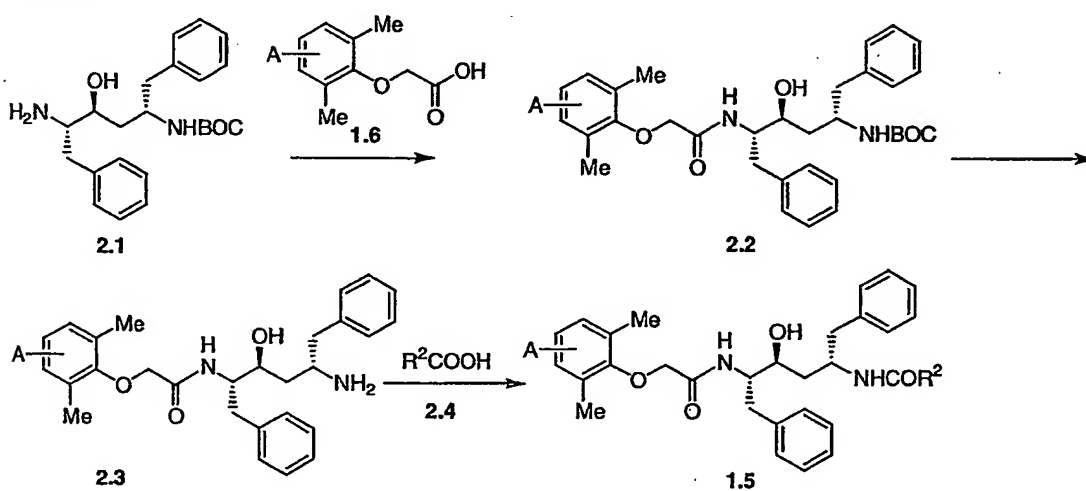
The free amine thus obtained is then reacted with the carboxylic acid R^2COOH 2.4, or an activated derivative thereof, to produce the amide 4.11. This reaction is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.5.

The reactions shown in Schemes 4 and 5 illustrate the preparation of the compounds 4.11 in which A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as, for example, optionally protected OH, SH, NH, as described below. Scheme 6 depicts the conversion of the compounds 4.11 in which A is OH, SH, NH, as described below, into the compounds 2. In this procedure, the compounds 4.11 are converted, using the procedures described below, Schemes 9-33, into the compounds 2.

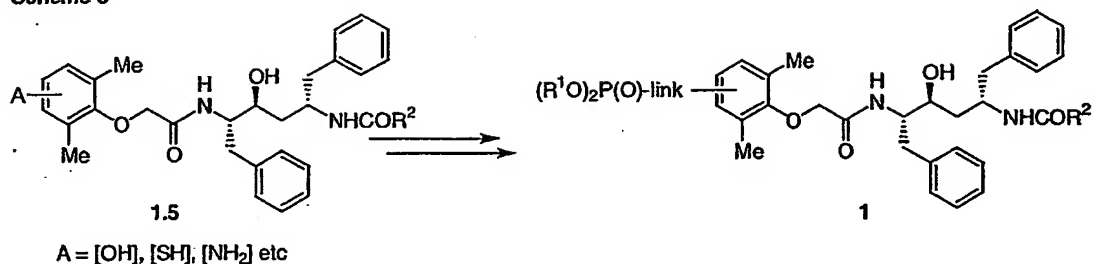
Scheme 1



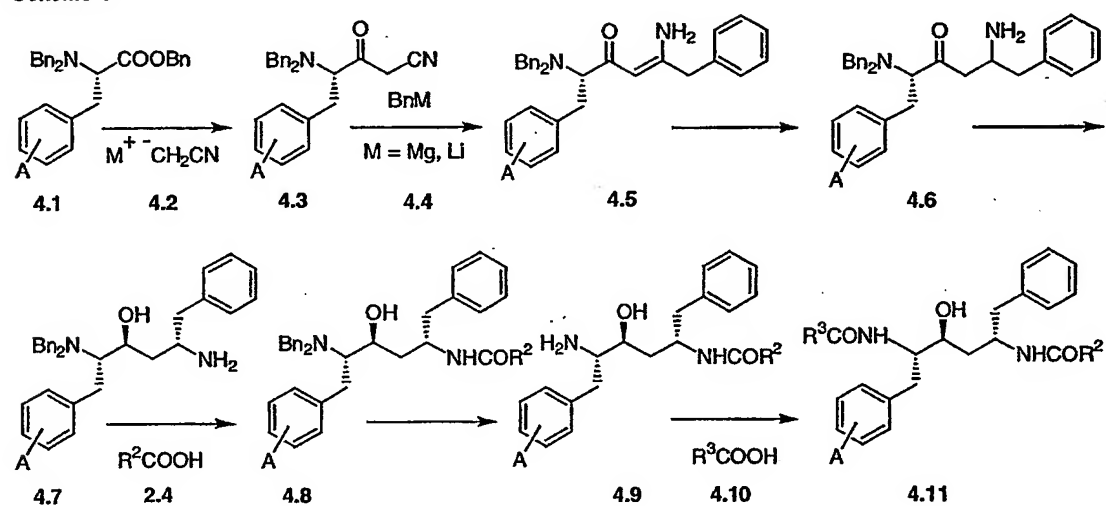
Scheme 2



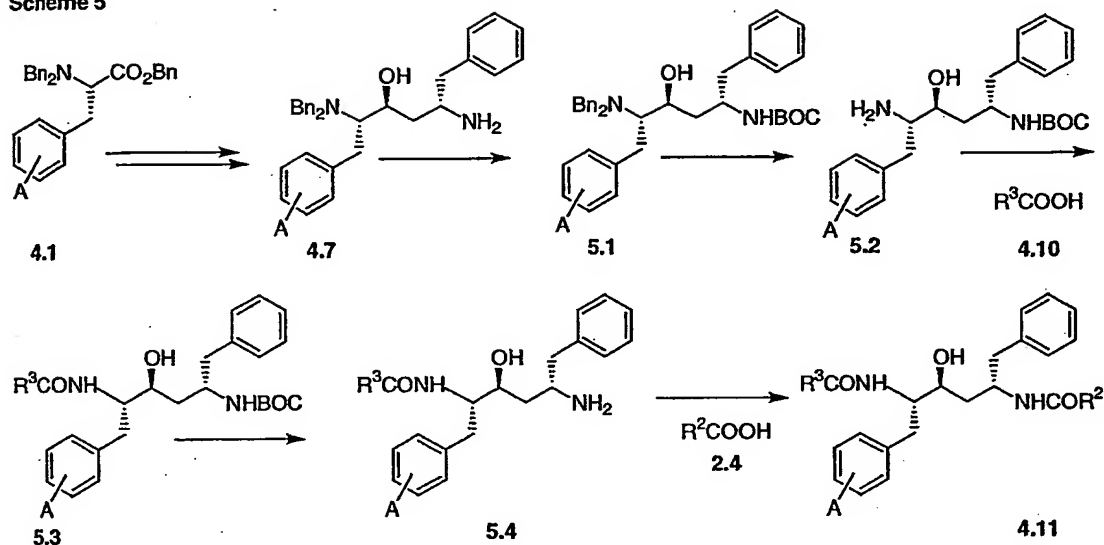
Scheme 3



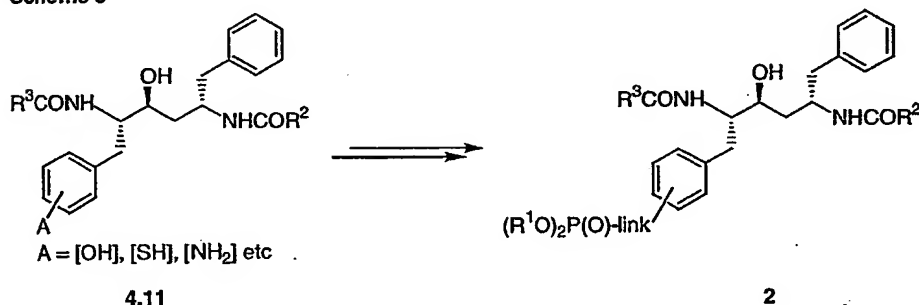
Scheme 4



Scheme 5



Scheme 6



Preparation of the phosphonate intermediates 3.

- 5 The phosphonate ester intermediate compounds 3 can be prepared by two alternative methods, illustrated in Schemes 7 and 8. The selection of the route to be employed for a given compound is made after consideration of the substituents which are present, and their stability under the reaction conditions required.

10 As shown in Scheme 7, 4-dibenzylamino-3-oxo-5-phenyl-pentanenitrile 7.1, the preparation of which is described in J. Org. Chem., 1994, 59, 4040, is reacted with a substituted benzylmagnesium halide reagent 7.2, in which the group B is a substituent, protected if appropriate, which can be converted, after the sequence of reactions shown in Scheme 7, into the substituent $\text{link-P}(\text{O})(\text{OR}^1)_2$. Examples of the substituent B are Br, $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}_2]$

[CHO] and the like; procedures for the transformation of these groups into the phosphonate moiety are shown below in Schemes 9-33.

The conditions for the reaction between the benzylmagnesium halide 7.2 and the ketonitrile 7.1 are similar to those described above for the preparation of the ketoenamine 4.5 (Scheme 4). Preferably, the ketonitrile 7.1 is reacted with three molar equivalents of the substituted benzylmagnesium chloride 7.2 in tetrahydrofuran at ca. 0°, to produce, after quenching by treatment with an organic carboxylic acid such as citric acid, as described in J. Org. Chem., 1994, 59, 4040, the ketoenamine 7.3.

The thus-obtained ketoenamine 7.3 is then transformed, via the intermediate compounds 7.4, 7.5, 7.6 and 7.7 into the diacylated carbinol 7.8. The conditions for each step in the conversion of the ketoenamine 7.3 to the diacylated carbinol 7.8 are the same as those described above (Scheme 4) for the transformation of the ketoenamine 4.5 into the diacylated carbinol 4.11. The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 9-33.

Alternatively, the phosphonate esters 3 can be obtained by means of the reactions illustrated in Scheme 8. In this procedure, the amine 7.4, the preparation of which is described above, (Scheme 7) is converted into the BOC derivative 8.1. The conditions for the introduction of the BOC group are similar to those described above for the conversion of the amine 4.7 into the BOC-protected product 5.1, (Scheme 5).

Preferably, the amine 7.4 is reacted with ca. 1.5 molar equivalents of BOC anhydride and excess potassium carbonate, in methyl tert-butyl ether, at ambient temperature, for example as described in US Patent 5914332, to yield the BOC-protected product 8.1.

The BOC-protected amine 8.1 is then converted, via the intermediates 8.2, 8.3 and 8.4 into the diacylated carbinol 7.8. The reaction conditions for this sequence of reactions are similar to those described above for the transformation of the BOC-protected amine 5.1 into the diacylated carbinol 4.11 (Scheme 5).

The diacylated carbinol 7.8 is then converted into the phosphonate ester 3, using procedures illustrated below in Schemes 18-20.

Preparation of dimethylphenoxyacetic acids incorporating phosphonate moieties.

Scheme 9 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-

5 dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol 9.1, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 9.2. Methods for the conversion of the substituent B into the group $\text{link-P(O)(OR}^1\text{)}_2$ are described below in

10 Schemes 9 - 33.

The protected phenolic hydroxyl group present in the phosphonate-containing product 9.2 is then deprotected, using methods described below, to afford the phenol 9.3.

The phenolic product 9.3 is then transformed into the corresponding phenoxyacetic acid 9.4, in a two step procedure. In the first step, the phenol 9.3 is reacted with an ester of

15 bromoacetic acid 9.5, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the

20 alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol 9.3 and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described

25 in US Patent 5914332, to afford the ester 9.6.

The thus-obtained ester 9.6 is then hydrolyzed to afford the carboxylic acid 9.4. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group,

30 methods for hydrolysis are described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product 9.6 which R is ethyl is hydrolyzed to the carboxylic acid 9.4 by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol 9.7, in which the substituent B is a precursor to the group link-P(O)(OR¹)₂, is transformed into the corresponding phenoxyacetic ester 9.8. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol 9.3 into the ester 9.6.

The phenolic ester 9.8 is then converted, by transformation of the group B into the group link-P(O)(OR¹)₂ followed by ester hydrolysis, into the carboxylic acid 9.4. The group B which is present in the ester 9.4 may be transformed into the group link-P(O)(OR¹)₂ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes 9-14 illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids 9.8, with, if appropriate, modifications made according to the knowledge of one skilled in the art..

Scheme 10 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds 10.4 are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde 10.1 and an aminoalkyl phosphonate ester 10.2. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 10.2 and the aldehyde component 10.1 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 10.3. The amination product 10.3 is then converted into the phenoxyacetic acid compound 10.4, using the alkylation and ester hydrolysis procedures described above, (Scheme 9) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde 10.5 (Aldrich) and a dialkyl aminoethyl phosphonate 10.6, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic

acid, as described, for example, in J. Amer. Chem. Soc., 91, 3996, 1969, to afford the amine product 10.3. The product is then converted into the acetic acid 10.8, as described above. Using the above procedures, but employing, in place of the aldehyde 10.5, different aldehydes 10.1, and/or different aminoalkyl phosphonates 10.2, the corresponding products 10.4 are
5 obtained.

In this and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 21)

10

Scheme 11 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol 11.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate 11.2. The
15 coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst. Following the coupling reaction, the product 11.3 is converted, using the procedures described
20 above, (Scheme 9) into the corresponding phenoxyacetic acid 11.4. Alternatively, the olefinic product 11.3 is reduced to afford the saturated 2,6-dimethylphenol derivative 11.5. Methods for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or
25 diimide. Following the reduction reaction, the product 11.5 is converted, as described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.6.

For example, 3-bromo-2,6-dimethylphenol 11.7, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether 11.8, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective
30 Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990 p. 77. The product 11.8 is reacted with an equimolar amount of a dialkyl allyl phosphonate 11.9, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of

bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product 11.10. The silyl group is removed, for example by the treatment of the ether 11.10 with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 11.11. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.12. Alternatively, the unsaturated compound 11.11 is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog 11.13. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 11.14.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol 11.7, different bromophenols 11.1, and/or different dialkyl alkenyl phosphonates 11.2, the corresponding products 11.4 and 11.6 are obtained.

Scheme 12 illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids 12.1 in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol 12.2 is converted, using the procedures illustrated in Scheme 9, into the corresponding 2,6-dimethylphenoxyacetic ester 12.3. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone 12.4, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of 11.3. (Scheme 11). The product 12.5 is then reduced catalytically, as described above for the reduction of 11.3, (Scheme 11), to afford the substituted cycloalkanone 12.6.

The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoethylphosphonate 12.7 and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate 12.8. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine 10.3 (Scheme 10). The resultant ester 12.8 is then hydrolyzed, as described above, to afford the phenoxyacetic acid 12.1.

For example, 4-bromo-2,6-dimethylphenol 12.9 (Aldrich) is converted, as described above, into the phenoxy ester 12.10. The latter compound is then coupled, in dimethylformamide

solution at ca. 60°, with cyclohexenone 12.11, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone 12.12. The enone is then reduced to the saturated ketone 12.13, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate 12.14, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine 12.15. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid 12.16.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol 12.9, different bromo-substituted 2,6-dimethylphenols 12.2, and/or different cycloalkenones 12.4, and/or different dialkyl aminoalkylphosphonates 12.7, the corresponding products 12.1 are obtained.

Scheme 13 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol 13.1 is reacted, in the presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate 13.2. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, 13.3 is then converted, as described above (Scheme 9) into the phenoxyacetic acid 13.4.

For example, 2,6-dimethyl-4-mercaptophenol 13.5, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate 13.6, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product 13.7. This compound is converted, employing the procedures described above, (Scheme 9) into the corresponding phenoxyacetic acid 13.8.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol 13.5, different hydroxy, thio or aminophenols 13.1, and/or different dialkyl bromoalkyl phosphonates 13.2, the corresponding products 13.4 are obtained.

Scheme 14 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-

5 dimethylphenol 14.1 is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound 14.2. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product 14.3. The product 14.3 is then converted, using the

10 procedures described above, (Scheme 9) into the phenoxyacetic ester 14.4. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite 14.5 at ca. 100° to afford the phosphonate ester 14.6. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product 14.6 is then converted into the acetic acid 14.7 by hydrolysis of the

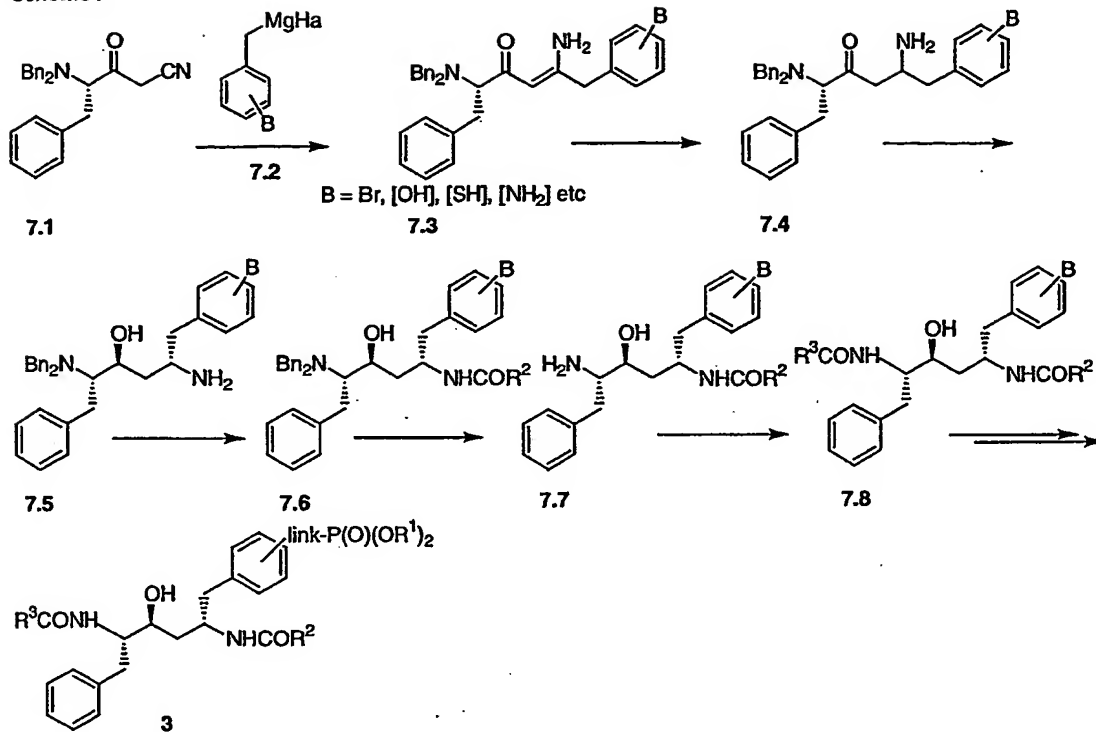
15 ester moiety, using the procedures described above, (Scheme 9).

For example, 4-hydroxy-2,6-dimethylphenol 14.8 (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J. Inorg. Chem., 1998, 2, 163, to afford the ether 14.10. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The

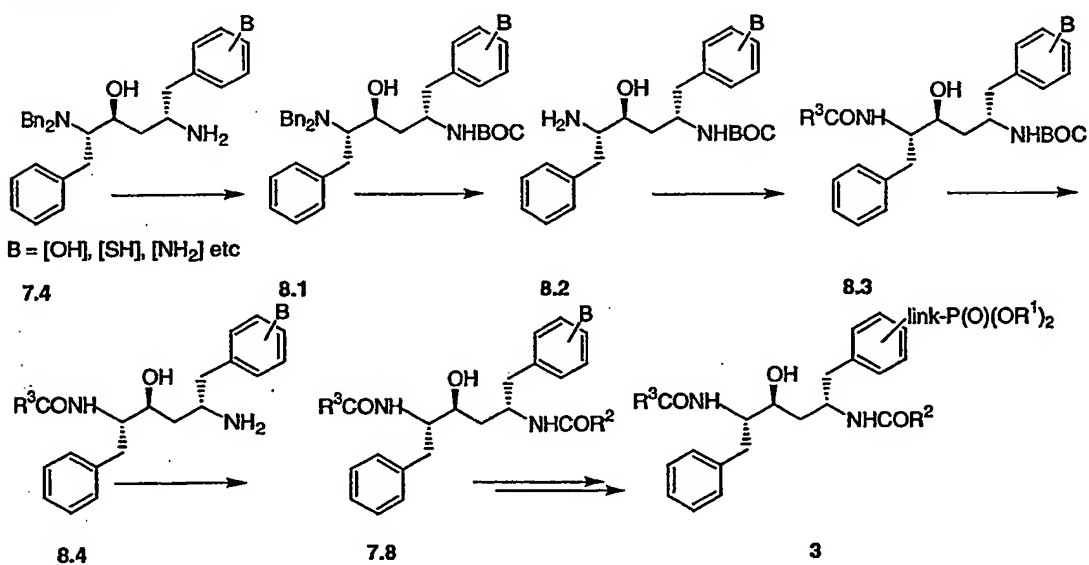
20 product 14.10 is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 9) to afford the phenoxyacetic ester 14.11. This product is heated at 100° for 3 hours with three molar equivalents of triethyl phosphite 14.12, to afford the phosphonate ester 14.13. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid 14.14.

25 Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine 14.9, different bis(halomethyl) aromatic or heteroaromatic compounds 14.2, and/or different hydroxy, mercapto or amino-substituted 2,6-dimethylphenols 14.1 and/or different trialkyl phosphites 14.5, the corresponding products 14.7 are obtained.

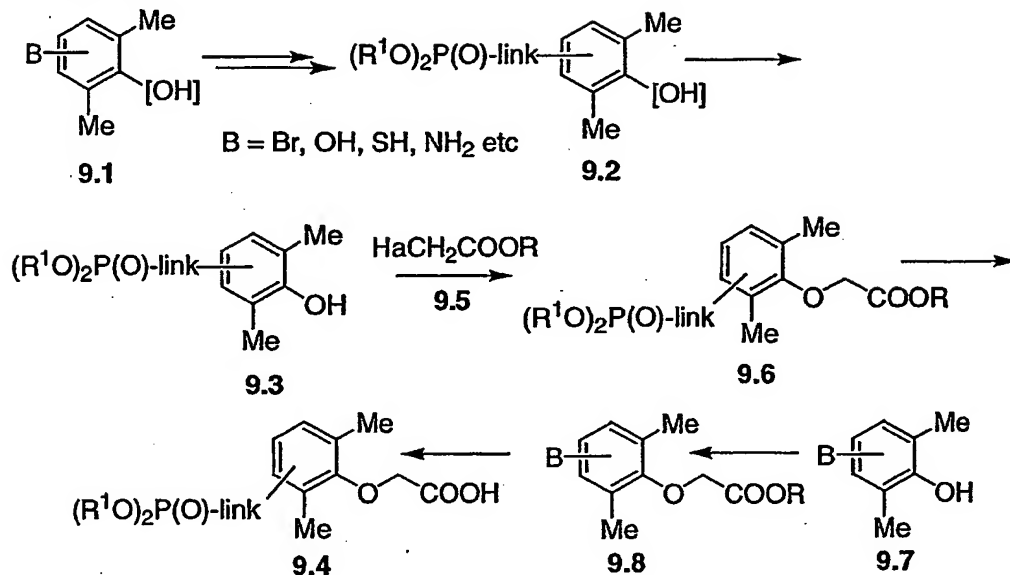
Scheme 7



Scheme 8

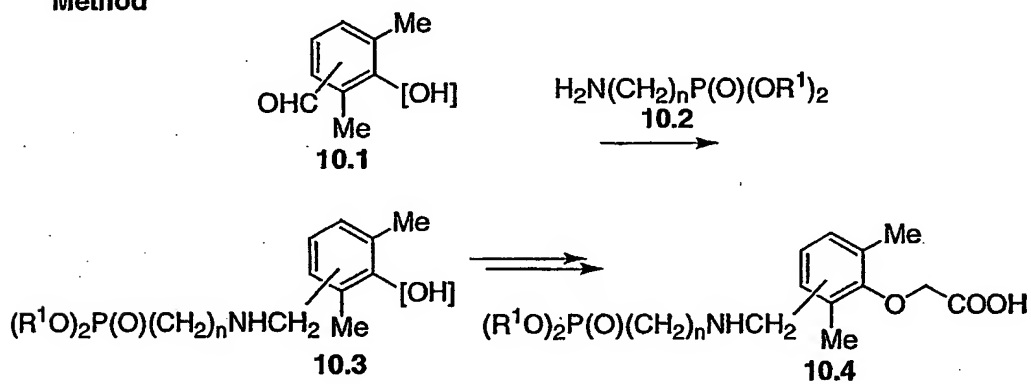


Scheme 9

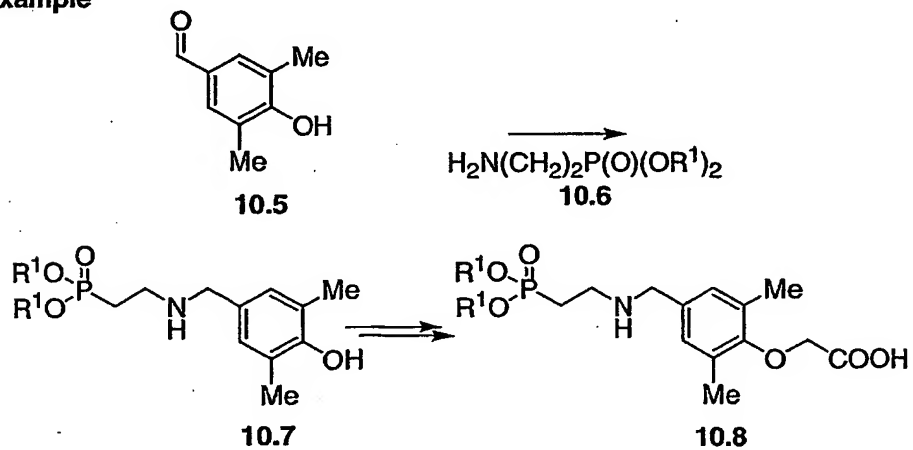


Scheme 10

Method

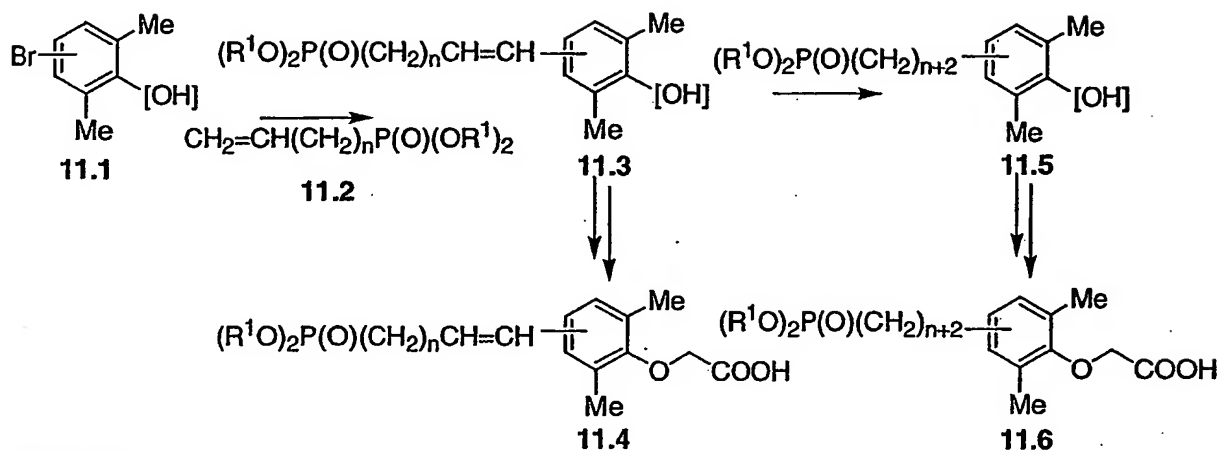


Example

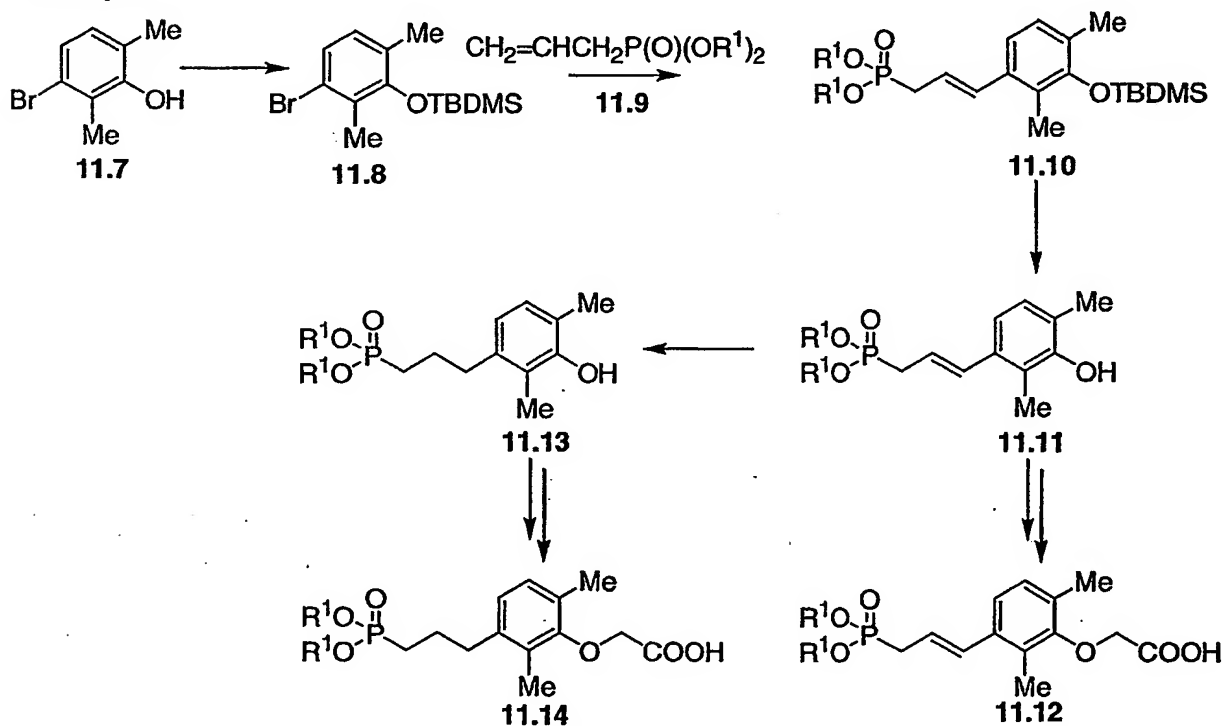


Scheme 11

Method

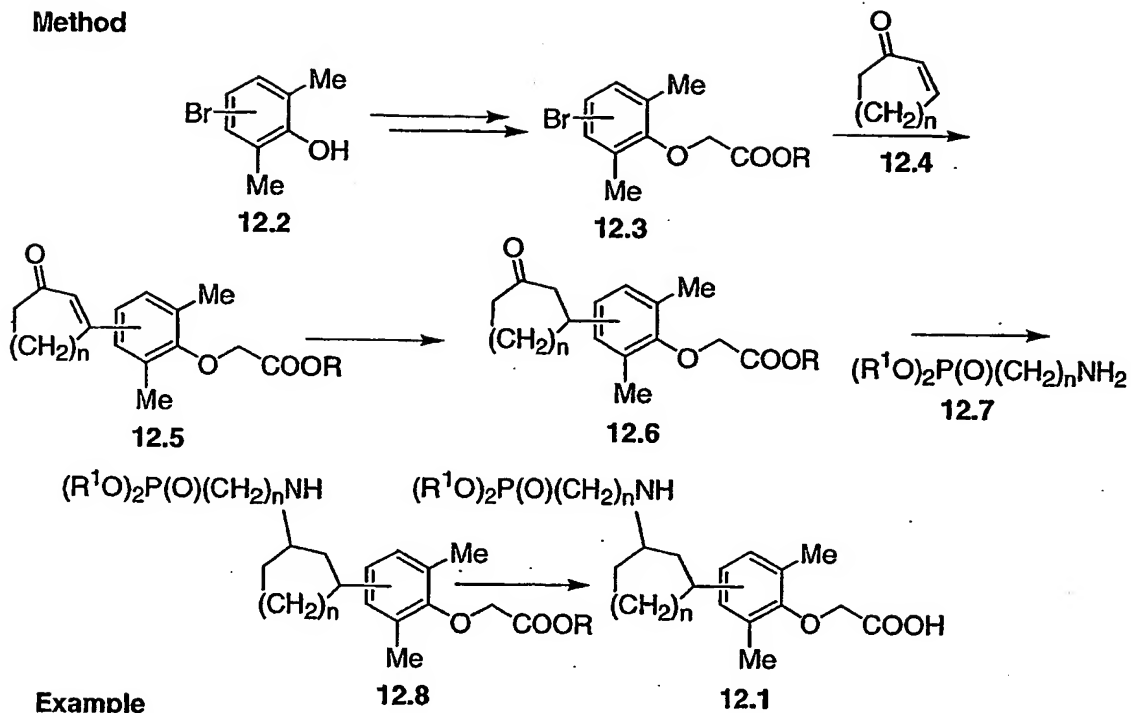


Example

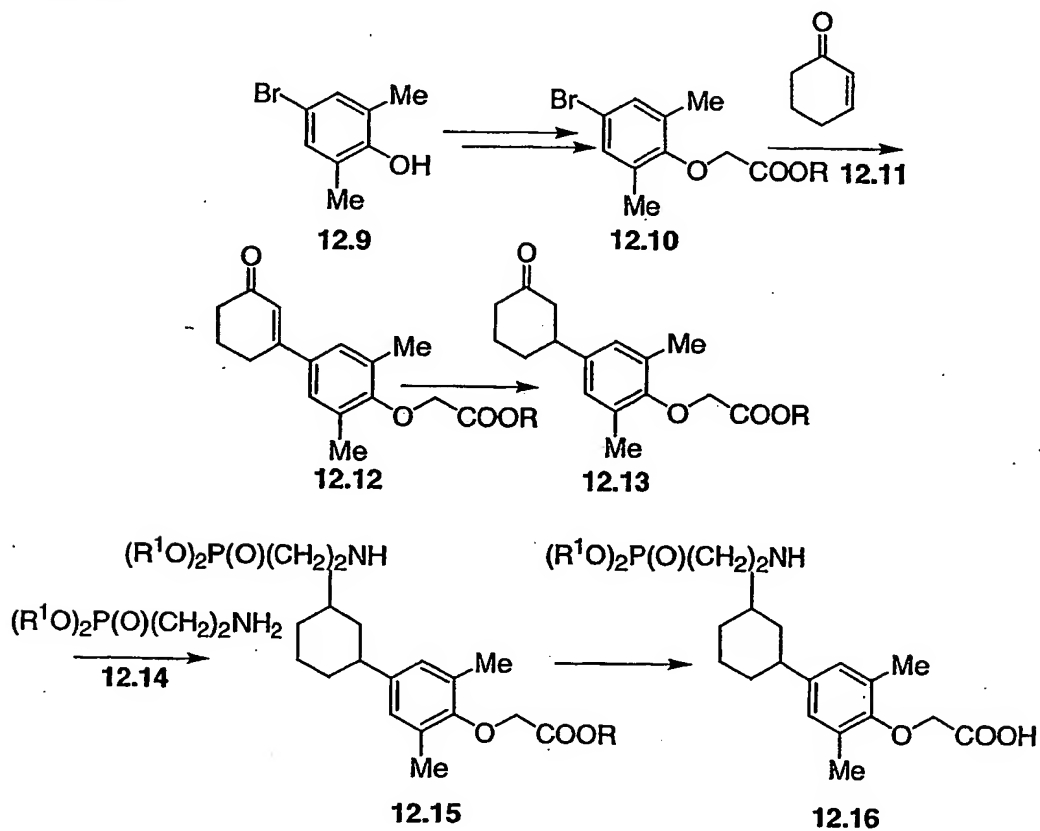


Scheme 12

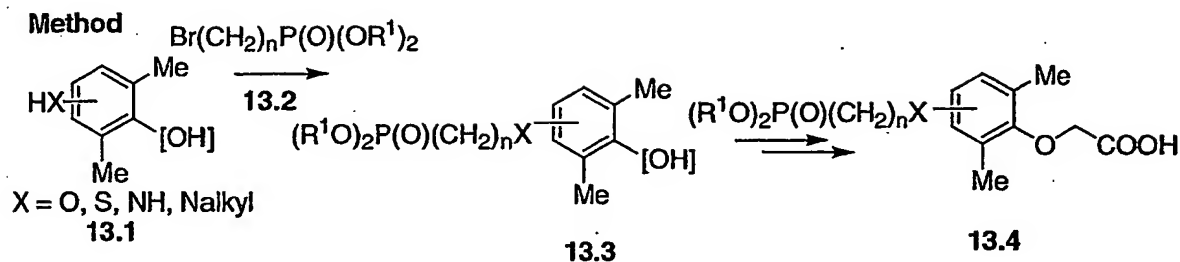
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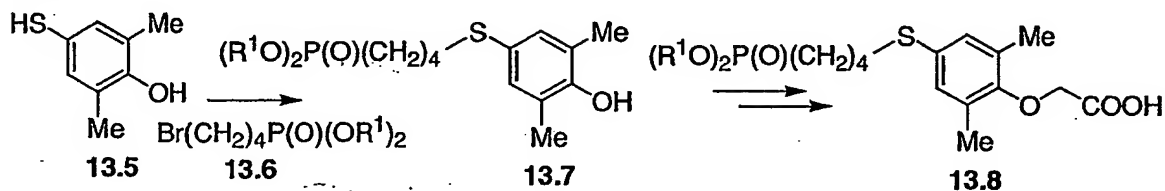
Example



Scheme 13

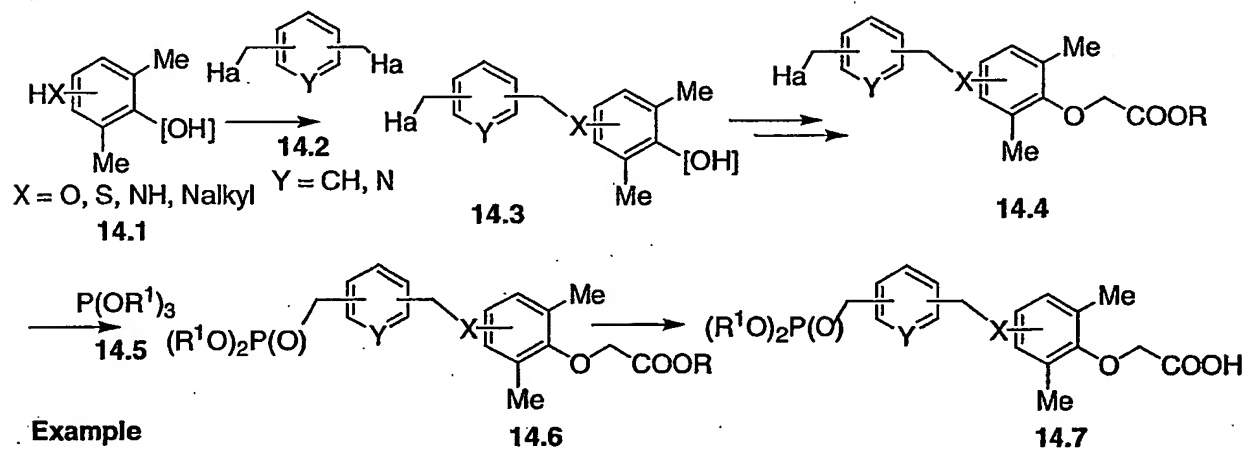


Example

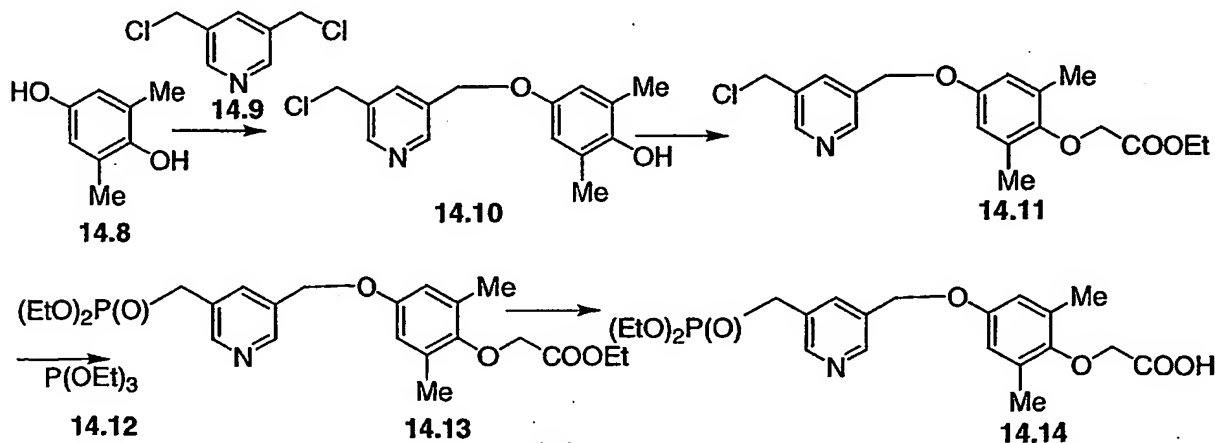


Scheme 14

Method



Example



Preparation of phenylalanine derivatives 4.1 incorporating phosphonate moieties, or precursors thereto.

5

Schemes 15-17 describe various methods for the preparation of phosphonate-containing analogs of phenylalanine. The compounds are then employed, as described above, (Schemes 4 and 5) in the preparation of the compounds 2.

10

Scheme 15 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 15.5.

15

In this procedure, a hydroxy or mercapto-substituted phenylalanine 15.1 is converted into the benzyl ester 15.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 15.2 is then protected. Protection methods for phenols and thiols are described respectively, for example, in Protective Groups in Organic Synthesis, by T.W.

20

Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 277. For example, suitable OH and SH protecting groups include tert-butyldimethylsilyl or tert-butyldiphenylsilyl.

25

Alternative SH protecting groups include 4-methoxybenzyl and S-adamantyl. The protected hydroxy- or mercapto ester 15.3 is then reacted with a benzyl or substituted benzyl halide and a base, for example as described in U.S. Patent 5,491,253, to afford the N, N-dibenzyl product 15.4. For example, the amine 15.3 is reacted at ca. 90° with two molar equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, to afford the tribenzylated product 15.4, as described in U.S. Patent 5,491,253. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in

30

Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p. 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient

temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl protecting groups are removed by treatment with mercuric trifluoroacetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol 15.5 is then reacted under various conditions to provide
5 protected phenylalanine derivatives 15.6, 15.7 or 15.8, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

As one option, the phenol or thiophenol 15.5 is reacted with a dialkyl bromoalkyl phosphonate 15.9 to afford the product 15.6. The alkylation reaction between 15.5 and 15.9 is effected in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium
10 carbonate or potassium carbonate. The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product 15.6.

For example, as illustrated in Scheme 15 Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, 15.12 is converted, as described above, into the benzyl ester 15.13.
15 The latter compound is then reacted with one molar equivalent of chloro tert-butyltrimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether 15.14. This compound is then converted, as described above, into the tribenzylated derivative 15.15. The silyl protecting group is removed by treatment of 15.15 with a tetrahydrofuran solution of tetrabutylammonium
20 fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 15.16. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 15.17 (Aldrich), in the presence of cesium carbonate, to afford the alkylated product 15.18.

Using the above procedures, but employing, in place of the 4-hydroxy phenylalanine 15.12,
25 different hydroxy or thio-substituted phenylalanine derivatives 15.1, and/or different bromoalkyl phosphonates 15.9, the corresponding ether or thioether products 15.6 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 15.5 is reacted with a dialkyl hydroxymethyl phosphonate 15.10 under the conditions of the
30 Mitsunobu reaction, to afford the ether or thioether compounds 15.7. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in

Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine.

- 5 For example, as shown in Scheme 15, Example 2, 3-mercaptophenylalanine 15.19, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester 15.20. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether 15.21. This compound is
- 10 then converted, as described above for the preparation of the tribenzylated phenylalanine derivative 15.4, into the tribenzyl derivative 15.22. The 4-methoxybenzyl group is then removed by the reaction of the thioether 15.22 with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J.Org. Chem., 52, 4420, 1987, to afford the thiol 15.23. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a
- 15 dialkyl hydroxymethyl phosphonate 15.24, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product 15.25. Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative 15.19, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or different dialkylhydroxymethyl phosphonates 15.10, the corresponding products 15.7
- 20 are obtained.

- Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 15.5 is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate 15.11 in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base
- 25 such as triethylamine or cesium carbonate, to afford the ether or thioether products 15.8. For example, as illustrated in Scheme 15, Example 3, 3-hydroxyphenylalanine 15.26 (Fluka) is converted, using the procedures described above, into the tribenzylated compound 15.27. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate 15.28, prepared as
- 30 described in Tet. Lett., 1986, 27, 1477, to afford the ether product 15.29. Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 15.26, different hydroxy or mercapto-substituted phenylalanines 15.1, and/or

different dialkyl trifluoromethanesulfonyloxymethylphosphonates 15.11, the corresponding products 15.8 are obtained.

5 Scheme 16 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a formyl-substituted tribenzylated phenylalanine derivative 16.1 and a dialkyl aminoalkylphosphonate 16.2.

10 In this procedure, a hydroxymethyl-substituted phenylalanine 16.3 is converted into the tribenzylated derivative 16.4 by reaction with three equivalents of a benzyl halide, for example, benzyl chloride, in the presence of an organic or inorganic base such as diazabicyclononene or potassium carbonate. The reaction is conducted in a polar solvent optionally in the additional presence of water. For example, the aminoacid 16.3 is reacted with three equivalents of benzyl chloride in aqueous ethanol containing potassium carbonate, as described in U.S.

15 Patent 5,491,253, to afford the product 16.4. The latter compound is then oxidized to afford the corresponding aldehyde 16.1. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product 16.1.

20 For example, the carbinol 16.4 is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in J. Org. Chem., 43, 2480, 1978, to yield the aldehyde 16.1. This compound is reacted with a dialkyl aminoalkylphosphonate 16.2 in the presence of a suitable reducing agent to afford the amine product 16.5. The preparation of amines by means of a reductive amination reaction is described above (Scheme 10).

25 For example, 3-(hydroxymethyl)-phenylalanine 16.6, prepared as described in Acta Chem. Scand. Ser. B, 1977, B31, 109, is converted, as described above, into the formylated derivative 16.8. This compound is then reacted, in ethanol, at ambient temperature, with one molar equivalent of a dialkyl aminoethylphosphonate 16.9, prepared as described in J. Org. Chem., 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated

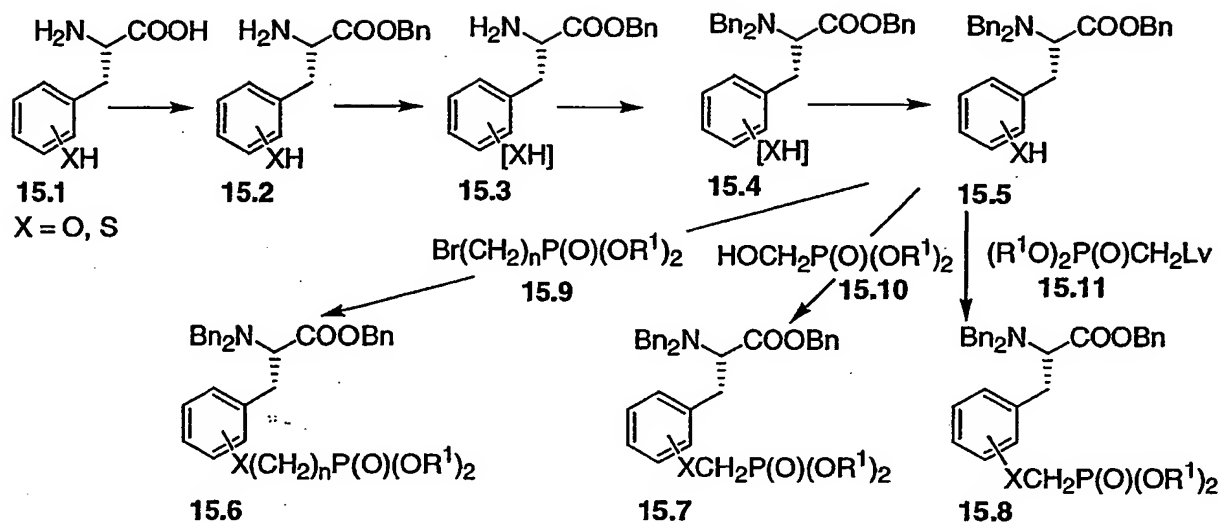
30 product 16.10.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 16.6, different hydroxymethyl phenylalanines 16.3, and/or different aminoalkyl phosphonates 16.2, the corresponding products 16.5 are obtained.

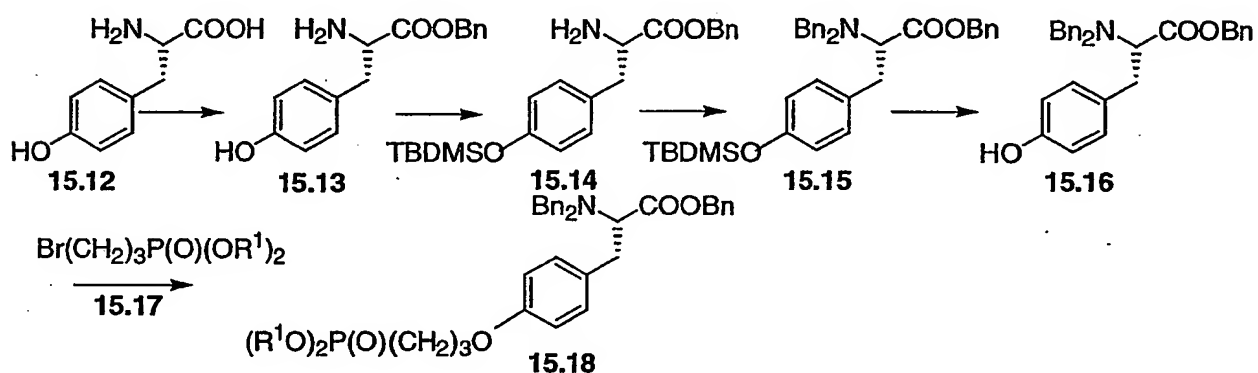
- 5 Scheme 17 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a suitably protected bromo-substituted phenylalanine 17.2 is coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 17.3 to produce the phosphonate ester 17.4. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.
- 10 For example, 3-bromophenylalanine 17.5, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 15) into the tribenzylated compound 17.6. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite 17.7, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 17.8.
- 15 Using the above procedures, but employing, in place of 3-bromophenylalanine 17.5, different bromophenylalanines 17.1, and/or different dialkylphosphites 17.3, the corresponding products 17.4 are obtained.

Scheme 15

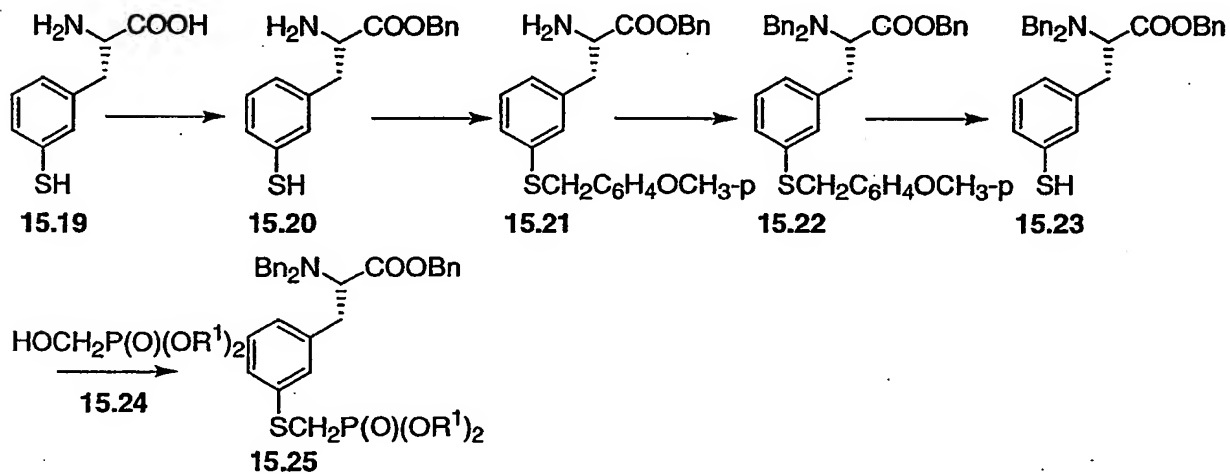
Method



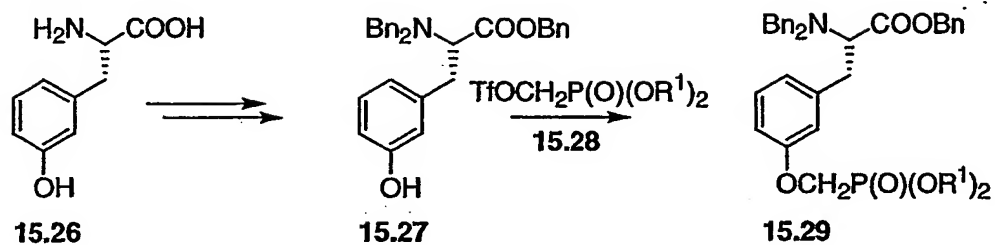
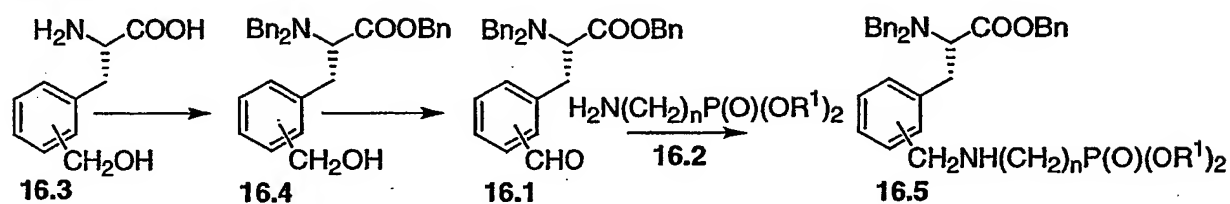
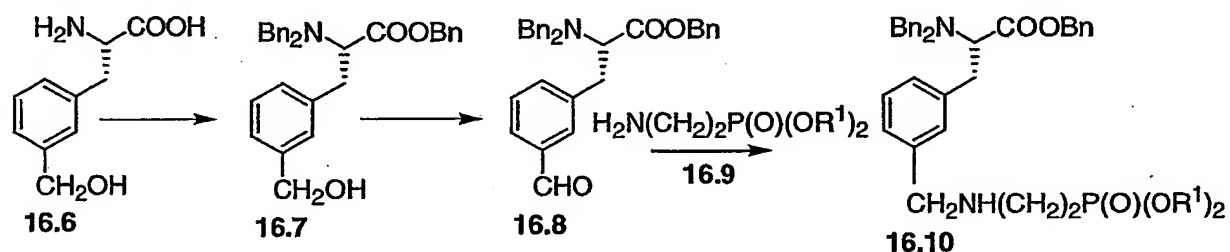
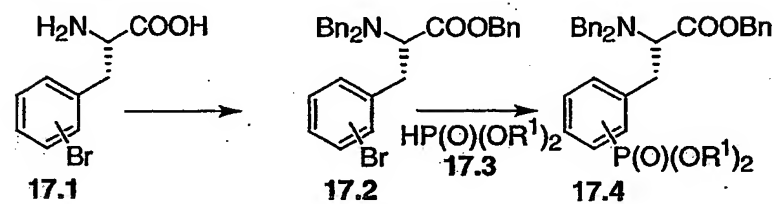
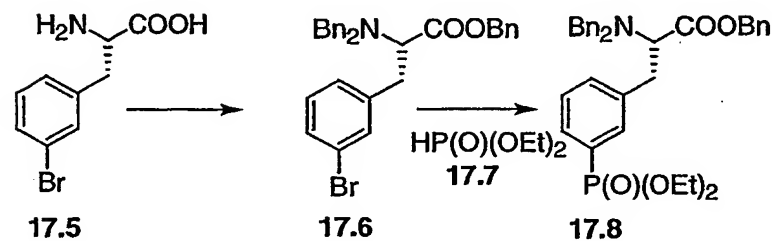
Example 1



Example 2



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Example 3**Scheme 16****Method****Example****Scheme 17****Example**

Preparation of phosphonate esters with structure 3.

Scheme 18 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, the ketonitrile 7.1, prepared as described in J. Org. Chem., 1994, 59, 4080, is reacted, as described above (Scheme n) with a bromobenzylmagnesium halide reagent 18.1. The resultant ketoenamine 18.2 is then converted into the diacylated bromophenyl carbinol 18.3. The conditions required for the conversion of the ketoenamine 18.2 into the carbinol 18.3 are similar to those described above (Scheme 7), for the conversion of the ketoenamine 7.3 into the carbinol 7.8. The product 18.3 is then reacted with a dialkyl phosphite 17.3, in the presence of a palladium (0) catalyst, to yield the phosphonate ester 3. The conditions for the coupling reaction are the same as those described above (Scheme 17) for the preparation of the phosphonate ester 17.8.

For example, the ketonitrile 7.1 is reacted, in tetrahydrofuran solution at 0°, with three molar equivalents of 4-bromobenzylmagnesium bromide 18.4, the preparation of which is described in Tetrahedron, 2000, 56, 10067, to afford the ketoenamine 18.5. The latter compound is then converted into the diacylated bromophenyl carbinol 18.6, using the sequence of reactions described above (Scheme 7) for the conversion of the ketoenamine 7.3 into the carbinol 7.8. The resultant bromo compound 18.6 is then reacted with diethyl phosphite 18.7 and triethylamine, in toluene solution at reflux, in the presence of tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 18.8.

Using the above procedures, but employing, in place of 4-bromobenzylmagnesium bromide 18.4, different bromobenzylmagnesium halides 18.1 and/or different dialkyl phosphites 17.3, there are obtained the corresponding phosphonate esters 3.

Scheme 19 illustrates the preparation of compounds 3 in which the phosphonate ester moiety is attached to the nucleus by means of a phenyl ring. In this procedure, a bromophenyl-substituted benzylmagnesium bromide 19.1, prepared from the corresponding bromomethyl compound by reaction with magnesium, is reacted with the ketonitrile 7.1. The conditions for this transformation are the same as those described above (Scheme 7). The product of the Grignard addition reaction is then transformed, using the sequence of reactions described

above, (Scheme 7) into the diacylated carbinol 19.2. The latter compound is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 17.3, to afford the phenylphosphonate 3. The procedure for the coupling reaction is the same as those described above for the preparation of the phosphonate 17.4.

- 5 For example, 4-(4-bromophenyl)benzyl bromide, prepared as described in DE 2262340, is reacted with magnesium to afford 4-(4-bromophenyl)benzylmagnesium bromide 19.3. This product is then reacted with the ketonitrile 7.1, as described above, to yield, after the sequence of reactions shown in Scheme 7, the diacylated carbinol 19.4. The latter compound is then reacted, as described above, (Scheme 17) with a diethyl phosphite 17.3, to afford the
10 phenylphosphonate 19.5.

Using the above procedures, but employing, in place of 4-(4-bromophenyl)benzyl bromide 19.3, different bromophenylbenzyl bromides 19.1, and/or different dialkyl phosphites 17.3, the corresponding products 3 are obtained.

- 15 Scheme 20 depicts the preparation of phosphonate esters 3 in which the phosphonate group is attached by means of a heteroatom and a methylene group. In this procedure, a hetero-substituted benzyl alcohol 20.1 is protected, affording the derivative 20.2. The protection of phenyl hydroxyl, thiol and amino groups are described, respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p.
20 277, 309. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, as
25 described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289. Amino groups can be protected, for example by dibenzylation. The conversion of amines into dibenzylamines, for example by treatment with benzyl bromide in a polar solvent such as acetonitrile or aqueous ethanol, in the presence of a base such as triethylamine or sodium carbonate, is described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 364. The resultant protected benzyl alcohol 20.2 is converted into a halo derivative 20.3, in which Ha is chloro or bromo. The conversion of alcohols into chlorides and bromides is described, for example, in

Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff.

For example, benzyl alcohols 20.2 can be transformed into the chloro compounds 20.3, in which Ha is chloro, by reaction with triphenylphosphine and N-chlorosuccinimide, as described in J. Am. Chem. Soc., 106, 3286, 1984. Benzyl alcohols can be transformed into
5 bromo compounds by reaction with carbon tetrabromide and triphenylphosphine, as described in J. Am. Chem. Soc., 92, 2139, 1970. The resultant protected benzyl halide 20.3 is then converted into the corresponding benzylmagnesium halide 20.4 by reaction with magnesium metal in an ethereal solvent, or by a Grignard exchange reaction treatment with an alkyl magnesium halide. The resultant substituted benzylmagnesium halide 20.4 is then converted,
10 using the sequence of reactions described above (Scheme 7) for the preparation of 7.8, into the carbinol 20.5 in which the substituent XH is suitably protected.

The protecting group is then removed to afford the phenol, thiophenol or amine 20.6.

Deprotection of phenols, thiophenols and amines is described respectively in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.

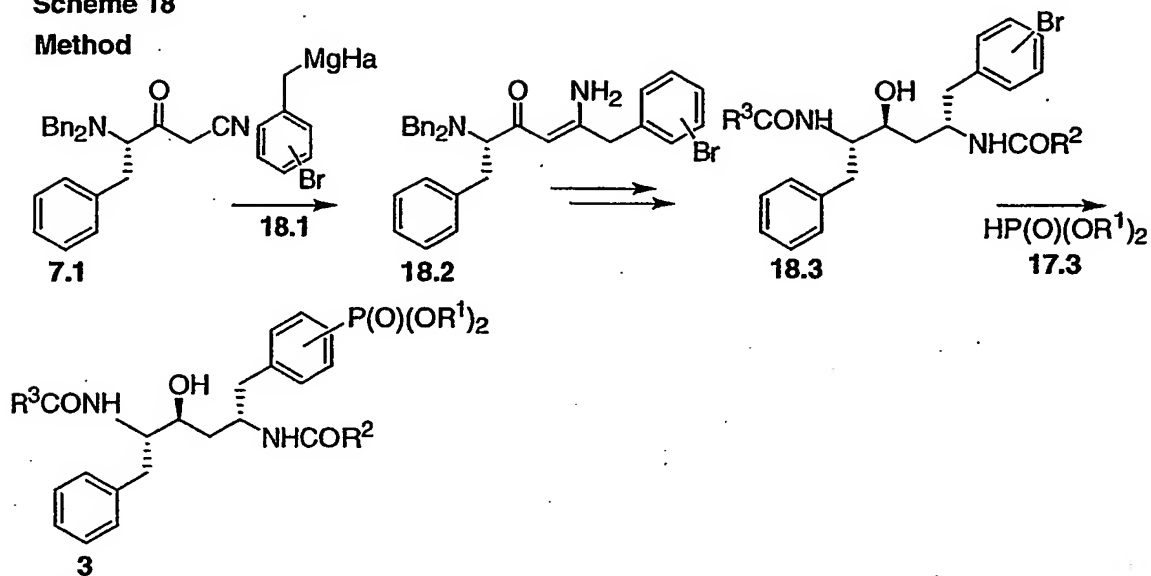
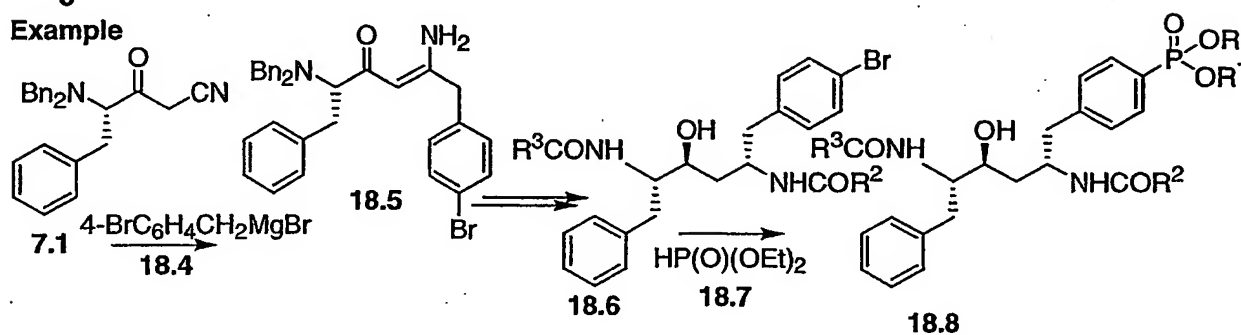
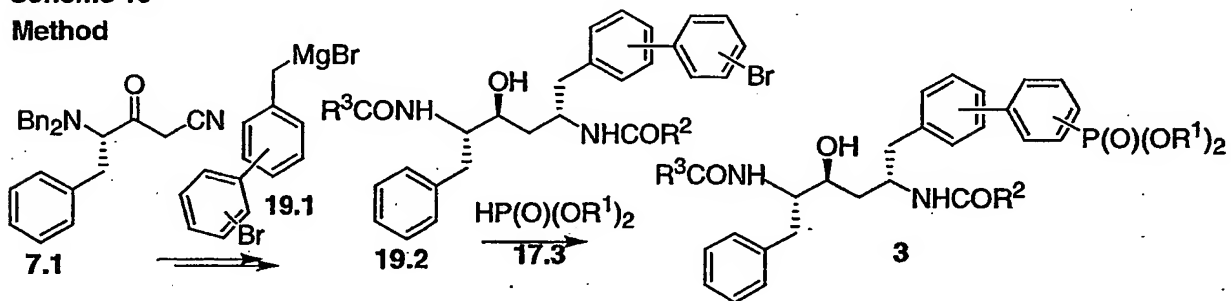
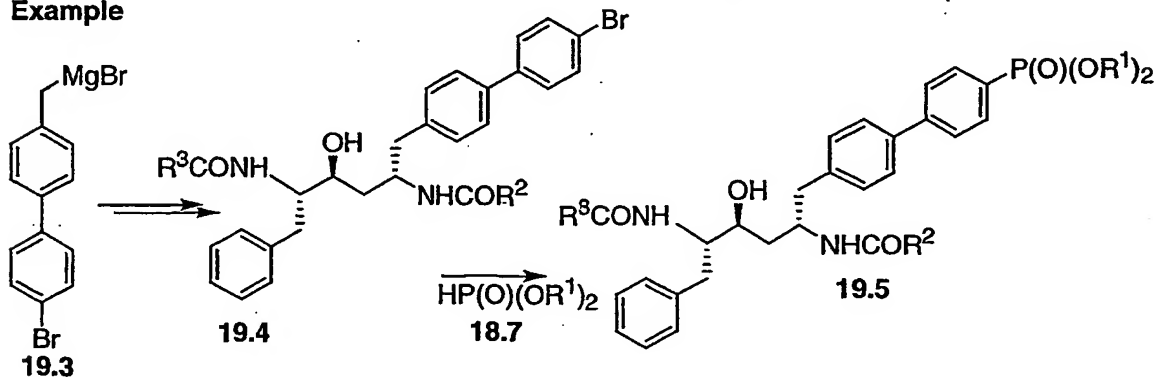
15 For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperature, as described in Chem. Pharm. Bull., 26, 1576, 1978. N,N-dibenzyl
20 amines can be converted into the unprotected amines by catalytic reduction in the presence of a palladium catalyst, as described above (Scheme 1). The resultant phenol, thiophenol or amine 20.6 is then converted into the phosphonate ester 3 by reaction with an activated derivative of a dialkyl hydroxymethyl phosphonate 15.11, in which Lv is a leaving group. The reaction is conducted under the same conditions as described above for the alkylation of the
25 phenol 15.5 to afford the ether or thioether 15.8 (Scheme 15).

For example, 3-hydroxybenzyl alcohol 20.7 (Aldrich) is reacted with chlorotriisopropylsilane and imidazole in dimethylformamide, as described in Tet. Lett., 2865, 1964, to afford the silyl ether 20.8. This compound is reacted with carbon tetrabromide and triphenylphosphine in dichloromethane, as described in J. Am. Chem. Soc., 109, 2738, 1987, to afford the

30 brominated product 20.9. This material is reacted with magnesium in ether to afford the Grignard reagent 20.10, which is then subjected to the series of reaction shown in Scheme 7 to afford the carbinol 20.11. The triisopropylsilyl protecting group is then removed by treatment

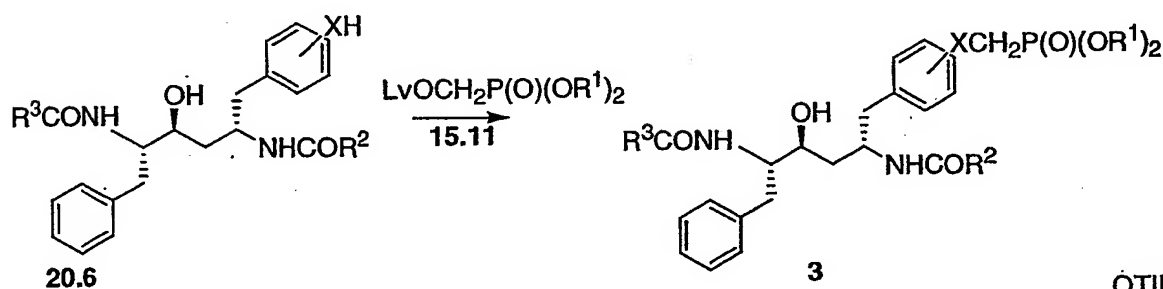
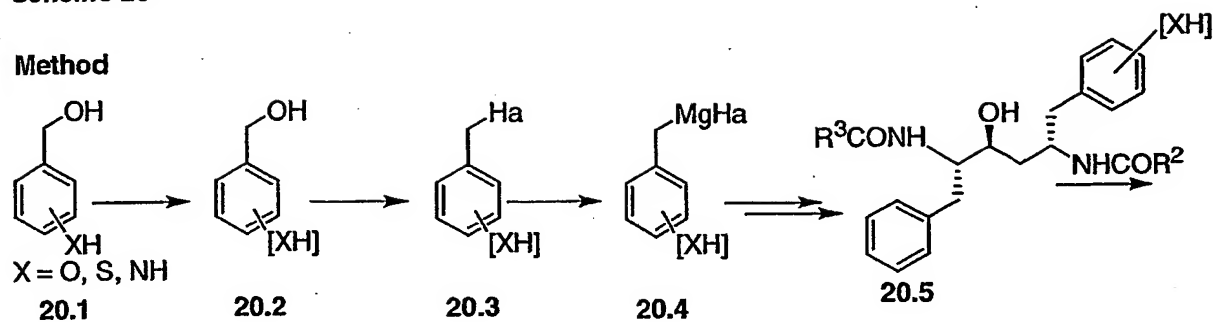
of the ether **20.11** with tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Org. Chem., 51, 4941, 1986. The resultant phenol **20.12** is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **15.28**, prepared as described in Synthesis, 4, 327, 1998, in the presence of a base such as dimethylaminopyridine,
5 as described above (Scheme 15) to afford the phosphonate product **20.13**.

Using the above procedures, but employing, in place of 3-hydroxybenzyl alcohol **20.7**, different hydroxy, mercapto or amino-substituted benzyl alcohols **20.1**, and/or different dialkyl hydroxymethyl phosphonate derivatives **15.11**, the corresponding products **3** are obtained.

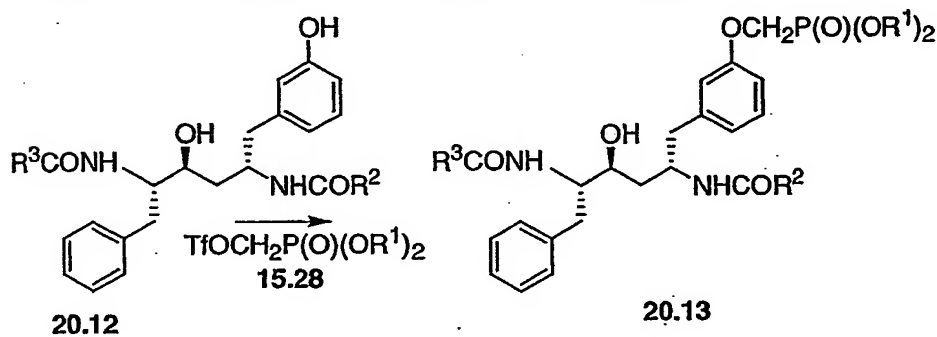
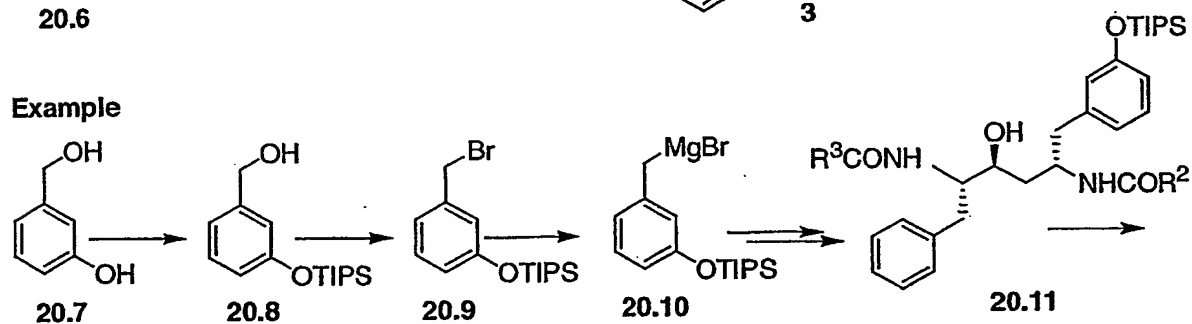
Scheme 18**Method****Example****Scheme 19****Method****Example**

Scheme 20

Method



Example



Schemes 1-33 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-5, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 21. The group R in Scheme 21 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-5 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-5. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 21.1 into the corresponding phosphonate monoester 21.2 (Scheme 21, Reaction 1) can be accomplished by a number of methods. For example, the ester 21.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 21.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 21.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 21.2 can be effected by treatment of the ester 21.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 21.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 21.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 21.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 21.1 or a phosphonate monoester 21.2 into the corresponding phosphonic acid 21.3 (Scheme 21, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 21.2 in which R¹ is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 21.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 21.2 in which R¹ is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 21.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters 21.1 in which R¹ is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 21.1 in which R¹ is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

The conversion of a phosphonate monoester 21.2 into a phosphonate diester 21.1 (Scheme 21, Reaction 4) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 21.2 is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 21.2 to the diester 21.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 15). The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 21.2 can be transformed into the phosphonate diester 21.1, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in which R¹ is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as

cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester 21.2 is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M.

- 5 Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester 21.1.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 21, Reaction 5) by means of the methods described above of for
10 the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1, except that only one molar proportion of the component R^1OH or R^1Br is employed.

- A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ 21.3 can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ 21.1 (Scheme 21, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and
15 triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids 21.3 can be transformed into phosphonic esters 21.1 in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is
20 reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 21.1.

Phosphonate esters 1-5 incorporating carbamate moieties.

- 25 The phosphonate esters 1-5 in which the R^2CO or R^3CO groups are formally derived from the carboxylic acid synthons C38 - C49 as shown in Chart 2c, contain a carbamate moiety. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p.
30 260ff.

Scheme 22 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 22, in the general reaction generating carbamates, a carbinol 22.1 is converted into the activated derivative 22.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 22.2 is then reacted with an amine 22.3, to afford the carbamate product 22.4. Examples 1 - 7 in Scheme 22 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 22, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 22.5. In this procedure, the carbinol 22.5 is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 22.6. The latter compound is then reacted with the amine component 22.3, in the presence of an organic or inorganic base, to afford the carbamate 22.7. For example, the chloroformyl compound 22.6 is reacted with the amine 22.3 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 22.7. Alternatively, the reaction is preformed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 22, Example 2 depicts the reaction of the chloroformate compound 22.6 with imidazole, 22.7, to produce the imidazolid 22.8. The imidazolid product is then reacted with the amine 22.3 to yield the carbamate 22.7. The preparation of the imidazolid is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 22 Example 3, depicts the reaction of the chloroformate 22.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 22.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 22.19 - 22.24 shown in Scheme 22, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 22.19, N-hydroxysuccinimide 22.20, or pentachlorophenol, 22.21, the mixed carbonate 22.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 22.22 or 2-hydroxypyridine 22.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

- 5 Scheme 22 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 22.8 is employed. In this procedure, a carbinol 22.5 is reacted with an equimolar amount of carbonyl diimidazole 22.11 to prepare the intermediate 22.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 22.8 is then reacted with an equimolar amount of the
- 10 amine R'NH₂ to afford the carbamate 22.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 22.7.

- Scheme 22, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 22.13. In this procedure, a carbinol ROH is reacted at ambient
- 15 temperature with an equimolar amount of benzotriazole carbonyl chloride 22.12, to afford the alkoxy carbonyl product 22.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. This product is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
- 20 to about 80° as described in Syn., 1977, 704.

- Scheme 22, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 22.14, is reacted with a carbinol 22.5 to afford the intermediate alkyloxycarbonyl intermediate 22.15. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate 22.7. The procedure in which the reagent 22.15 is derived from
- 25 hydroxybenzotriazole 22.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 22.15 is derived from N-hydroxysuccinimide 22.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 22.15 is derived from 2-hydroxypyridine 22.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 22.15 is derived from 4-nitrophenol 22.24 is described in Syn. 1993, 103. The reaction between equimolar amounts
- 30 of the carbinol ROH and the carbonate 22.14 is conducted in an inert organic solvent at ambient temperature.

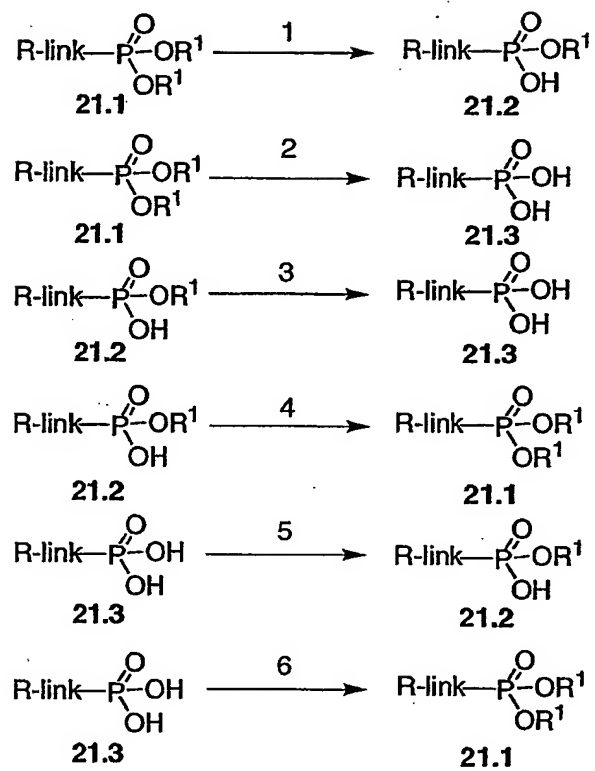
Scheme 22, Example 7 illustrates the preparation of carbamates from alkoxy carbonyl azides 22.16. In this procedure, an alkyl chloroformate 22.6 is reacted with an azide, for example sodium azide, to afford the alkoxy carbonyl azide 22.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 22.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme 22, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 22.7.

Scheme 22, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 22.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 22.7.

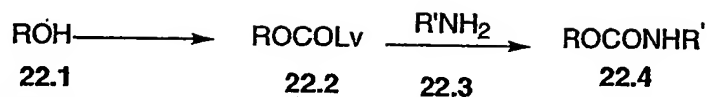
Scheme 22, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 22.7.

Scheme 21

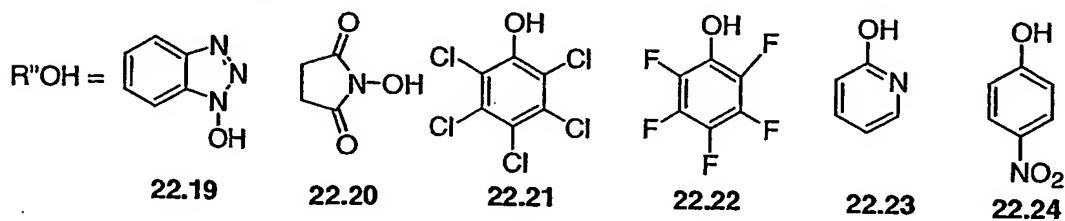
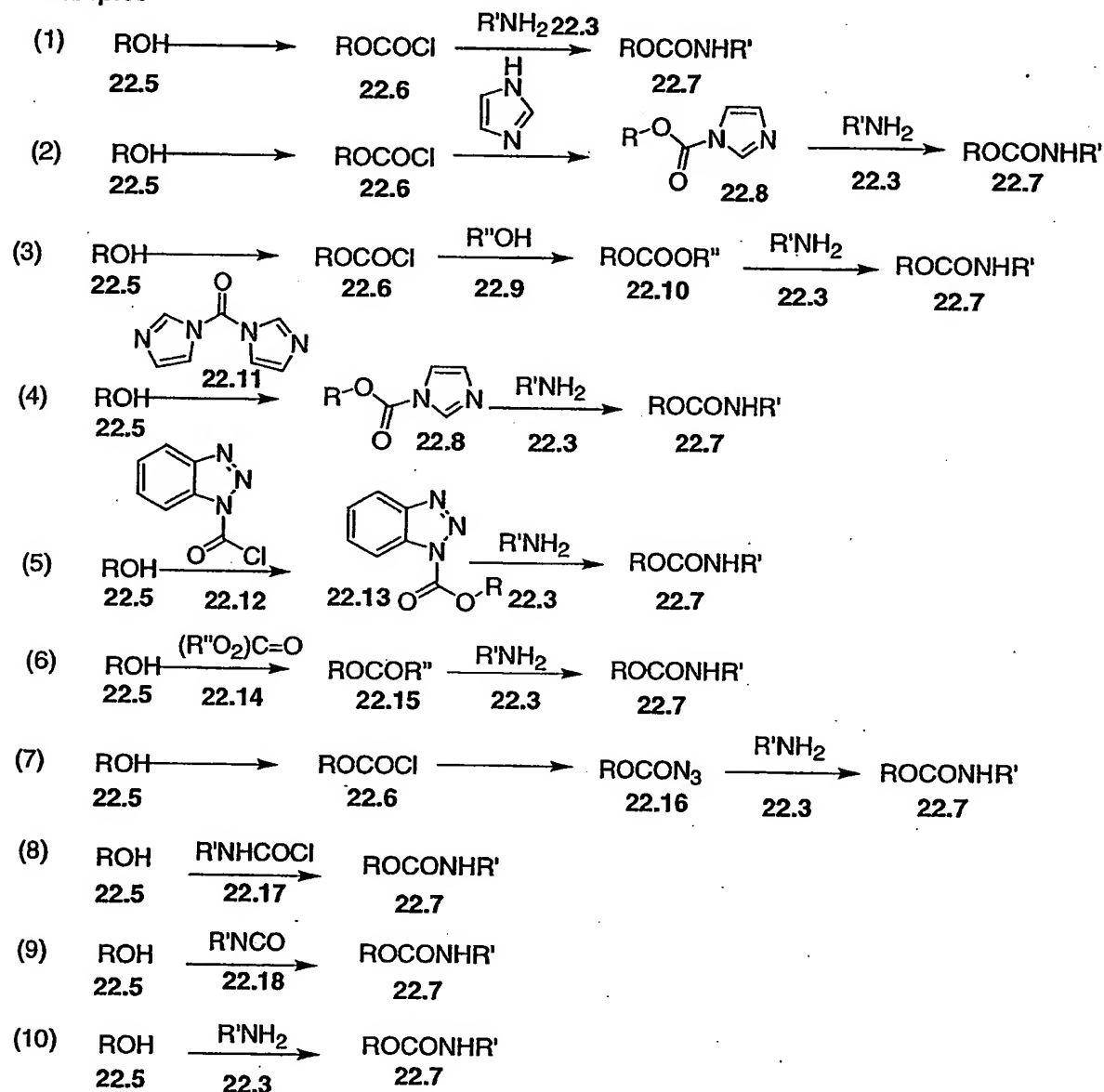


Scheme 22

General reaction



Examples



Preparation of phosphonate intermediates 4 and 5 with phosphonate moieties incorporated into the groups R^2COOH and R^3COOH .

5 The chemical transformations described in Schemes 1-22 illustrate the preparation of compounds 1-3 in which the phosphonate ester moiety is attached to the dimethylphenoxyacetyl (R^3) substructure, (Schemes 1-3), the phenylalanine moiety (Schemes 4-6), and the benzyl moiety (Schemes 7, 8).

The various chemical methods employed herein (Schemes 9-22) for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^3COOH , as defined in Charts 2a, 2b, and 2c. The resultant phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 4 and 5. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{3a}COOH$ are the same as those described above (Schemes 4, 5 and 22) for the introduction of the R^2CO and R^3CO moieties.

For example, Schemes 23 - 27 illustrate methods for the preparation of hydroxymethyl-substituted benzoic acids (structure C25, Chart 2b) incorporating phosphonate moieties; Schemes 28-30 illustrate the preparation of tetrahydropyrimidine aminoacid derivatives (structure C27, Scheme 2b) incorporating phosphonate ester moieties, and Schemes 31-33 show the syntheses of benzyl carbamate aminoacid derivatives (structure C4, Chart 2a) incorporating phosphonate ester moieties. The thus-obtained phosphonate ester synthons are then incorporated into the compounds 4 and 5.

Scheme 23 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 23.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 23.2. This compound is reacted with a chlorodialkyl phosphite 23.3 to yield the phenylphosphonate ester 23.4, which upon deprotection affords the carboxylic acid 23.5.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, 23.6, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Amer. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The

acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane 23.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester 23.8. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester 23.9, known as the OBO ester. This material is treated with a
5 silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether 23.10. Halogen-metal exchange is performed by the reaction of 23.10 with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite 23.3, to produce the phosphonate 23.11. Deprotection, for example
10 by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid 23.12.

Using the above procedures, but employing, in place of the bromo compound 23.6, different bromo compounds 23.1, there are obtained the corresponding products 23.5.

15 Scheme 24 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

In this method, a suitably protected dimethyl hydroxybenzoic acid, 24.1, is reacted with a brominating agent, so as to effect benzylic bromination. The product 24.2 is reacted with a sodium dialkyl phosphite, 24.3, as described in J. Med. Chem., 1992, 35, 1371, to effect
20 displacement of the benzylic bromide to afford the phosphonate 24.4. Deprotection of the carboxyl function then yields the carboxylic acid 24.5.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, 24.6, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition
25 1990, p17, to afford the ether ester 24.7. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product 24.7 is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product 24.8. This compound is then reacted with a sodium dialkyl
30 phosphite 24.3 in tetrahydrofuran, as described above, to afford the phosphonate 24.9. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid 24.10.

Using the above procedures, but employing, in place of the methyl compound 24.6, different methyl compounds 24.1, there are obtained the corresponding products 24.5.

Scheme 25 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxymethyl benzoic acid 25.1 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate 25.2, to afford the coupled product 25.3, which upon deprotection affords the carboxylic acid 25.4.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 25.6, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 25.7, by treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 77, to afford the mono-silyl ether 25.8. This compound is then reacted with a dialkyl hydroxymethylphosphonate 25.2, under the conditions of the Mitsunobu reaction, as described above (Scheme 15) to afford the coupled product 25.9. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic carboxylic acid 25.10.

Using the above procedures, but employing, in place of the phenol 25.6, different phenols or thiophenols 25.1, there are obtained the corresponding products 25.4.

Scheme 26 depicts the preparation of phosphonate esters attached to the

hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 26.2 is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 26.1. The product 26.3 can be deprotected to afford the phosphonate 26.4, or subjected to catalytic hydrogenation to afford the saturated compound, which upon deprotection affords the corresponding carboxylic acid 26.5.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 26.6, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester 26.7. This

compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 26.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above (Scheme 11) to afford the product 26.9. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products 26.10 and 26.11.

Using the above procedures, but employing, in place of the bromo compound 26.6, different bromo compounds 26.1, and/or different phosphonates 26.2, there are obtained the corresponding products 26.4 and 26.5.

Scheme 27 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 27.1 is converted to the corresponding boronic acid 27.2, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 27.3. The product 27.4 is then deprotected to afford the diaryl phosphonate product 27.5.

For example, the silylated OBO ester 27.6, prepared as described above, (Scheme 23), is converted into the boronic acid 27.7, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate 27.8, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate 27.9. Deprotection, as described above, then affords the benzoic acid 27.10.

Using the above procedures, but employing, in place of the bromo compound 27.6, different bromo compounds 27.1, and/or different phosphonates 27.3, there are obtained the corresponding carboxylic acid products 27.5.

Scheme 28 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid C27 in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom O, S, or N. In this procedure, an amino acid 28.1, in which R⁴ is as defined in Chart 2b, is converted into the corresponding phenyl carbamate 28.2. The preparation of phenyl carbamates is described in Tet. Lett., 1977, 1936, and in J. Chem. Soc., C, 1967, 2015. The amine substrate is reacted with phenyl chloroformate in the presence of an inorganic or

organic base, such as potassium carbonate or triethylamine, in an organic, aqueous or aqueous organic solvent such as dichloromethane, tetrahydrofuran or water or pyridine. Preferably, the aminoacid 28.1 is reacted with phenyl chloroformate, in water containing lithium hydroxide, lithium chloride and alumina, at a pH of about 9.5, as described in Org. Process Res. Dev., 2000, 4, 264, to afford the phenyl carbamate 28.2. This compound is then reacted with di(3-chloropropyl)amine 28.3, prepared as described in Tet. 1995, 51, 1197, to afford the amide product 28.4. The preparation of amides by reaction of an ester with an amide is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 987. The displacement reaction is effected by treatment of the substrate with the amine, optionally in the presence of a base such as sodium methoxide and the like, to afford the amide product 28.4. Preferably, the carbamate 28.2 and the amine 28.3 are reacted together in tetrahydrofuran, in the presence of sodium hydroxide or lithium hydroxide, to produce the amide product 28.4. The latter compound is then transformed, optionally without isolation, into the chloropropyl-substituted tetrahydropyrimidine product 28.5, by reaction with a strong base such as potassium tert. butoxide in tetrahydrofuran, as described in Org. Process. Res. Dev., 2000, 4, 264. The compound 28.5 is then reacted with a dialkyl hydroxy, mercapto or alkylamino-substituted alkylphosphonate 28.6 to afford the displacement product 28.7. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as sodium hydride, lithium hexamethyldisilazide, potassium carbonate or the like, optionally in the presence of a catalytic amount of potassium iodide, to afford the ether, thioether or amine product 28.7.

Alternatively, the chloropropyl-substituted tetrahydropyrimidine compound 28.5 is transformed into the corresponding propylamine 28.8. The conversion of halo derivatives into amines is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 397ff, or Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 665ff. The chloro compound is reacted with ammonium hydroxide, anhydrous ammonia or hexamethylene tetramine, or with an alkali metal amide such as sodamide to afford the amine product. Preferably, the chloro compound is reacted with potassium phthalimide, and the phthalimido product is then cleaved by treatment with hydrazine, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953 p. 679, to afford the amine 28.8. The product is then subjected to a reductive amination reaction with a dialkyl formylalkyl phosphonate 28.9, to yield the phosphonate product 28.10.

For example, as shown in Scheme 28, Example 1, 3-methyl-2-phenoxy-carbonylamino-butyr-
ic acid 28.11, prepared as described in Org. Process Res. Dev., 2000, 4, 264, is reacted with
di(3-chloropropyl)amine, using the conditions described above, to afford 2-[3,3-bis-(3-chloro-
propyl)-ureido]-3-methyl-butyr-ic acid 28.4. The product is then reacted sequentially with
5 sodium hydroxide and then potassium tert. butoxide in tetrahydrofuran, as described in Org.
Process Res. Dev., 2000, 4, 264, so as to afford the cyclized product 2-[3-(3-chloro-propyl)-
2-oxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyr-ic acid 28.13. The latter compound is then
reacted in dimethylformamide solution at about 70°, with a dialkyl 2-mercaptoethyl
phosphonate 28.14, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, potassium
10 carbonate and a catalytic amount of potassium iodide, to yield the phosphonate ester 28.13.
Using the above procedures, but employing, in place of the valine carbamate 28.11, different
carbamates 28.2, and/or different hetero-substituted alkyl phosphonates 28.6, the
corresponding products 28.7 are obtained.

As a further illustration, Scheme 28, Example 2 depicts the reaction of the chloropropyl
15 tetrahydropyrimidine derivative 28.13 with potassium phthalimide 28.16. Equimolar amounts
of the reactants are combined in dimethylformamide at ca 80°, in the presence of a catalytic
amount of potassium iodide, to afford 2-[3-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-
2-oxo-tetrahydro-pyrimidin-1-yl]-3-methyl-butyr-ic acid 28.17. The product is then reacted
under reductive amination conditions, as described above (Scheme 10) with a dialkyl
20 formylphenyl phosphonate 28.19 (Epsilon) to yield the phosphonate ester product 28.20.
Using the above procedures, but employing, in place of the valine carbamate 28.11, different
carbamates 28.2, and/or different formyl-substituted alkyl phosphonates 28.9, the
corresponding products 28.10 are obtained.

25 Scheme 29 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid
C27 in which the phosphonate moiety is attached by means of an alkylene chain. In this
procedure, an aminoacid 29.1 is subjected to an alkylation reaction with a propanol derivative
29.2 in which Lv is a leaving group such as halo or sulfonyl. The reaction is conducted in
aqueous or aqueous organic solution in the presence of a base such as sodium hydroxide,
30 potassium carbonate and the like, to afford the product 29.3. This compound is then oxidized
to the corresponding aldehyde 29.4. The conversion of alcohols to aldehydes is described, for
example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff.

Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as pyridine, dichloromethane or toluene. Preferably, the alcohol 29.3 is reacted with an equimolar amount of pyridinium chlorochromate in dichloromethane at ambient temperature, to afford the aldehyde 29.4. This material is then subjected to a reductive amination reaction with a dialkyl aminoalkyl phosphonate 29.5, using the conditions described above (Scheme 10) to produce the phosphonate ester 29.6. The latter compound is then reacted with phosgene, or carbonyldiimidazole or an equivalent reagent, to yield the tetrahydropyrimidine product 29.7. Equimolar amounts of the reagents are combined in an inert polar solvent such as tetrahydrofuran or dimethylformamide at ambient temperature, to effect the cyclization reaction.

For example, 2-(3-hydroxy-propylamino)-3-methyl-butyric acid, the preparation of which is described in Toxicol. Appl. Pharm., 1995, 131, 73, is oxidized, as described above, to afford 3-methyl-2-(3-oxo-propylamino)-butyric acid 29.9. The product is then reacted with a dialkyl aminoethyl phosphonate 29.10, the preparation of which is described in J. Org. Chem., 2000, 65, 676, under reductive amination conditions, to give the product 29.11. This compound is then reacted one molar equivalent of carbonyldiimidazole in dichloromethane, as described in US Patent 5914332, to afford the tetrahydropyrimidine product 29.12.

Using the above procedures, but employing, in place of the valine derivative 29.8, different aminoacid derivatives 29.3, and/or different amino-substituted alkyl phosphonates 29.5, the corresponding products 29.7 are obtained.

Scheme 30 illustrates the preparation of analogs of the tetrahydropyrimidine carboxylic acid C27 in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a tetrahydropyrimidine aminoacid derivative, prepared as described in U.S. Patent 5,914,332, is converted into the carboxyl-protected compound 30.2. The protection and deprotection of carboxyl groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990, p. 224ff. For example, the carboxyl group is protected as a benzyl or substituted benzyl ester, removable by means of hydrogenolysis, or as a tert. butyl ester, removable by treatment with anhydrous acid. The carboxyl-protected derivative 30.2 is then reacted with a dialkyl bromoalkyl phosphonate 30.3, in the presence of a strong base such as sodium hydride, potassium tert. butoxide, lithium

hexamethyldisilazide and the like, in a polar solvent such as dimethylformamide, to afford the alkylation product 30.4. The carboxyl group is then deprotected to yield the carboxylic acid 30.5.

For example, 3-methyl-2-(3-methyl-2-oxo-tetrahydro-pyrimidin-1-yl)-butyric acid 30.6, prepared as described in Org. Process Res. Dev., 200, 4, 264, is converted into the benzyl ester 30.7 by reaction with benzyl alcohol, dicyclohexylcarbodiimide and dimethylaminopyridine in dichloromethane, as described in J. Chem. Soc. Chem. Comm., 1982, 1132. The product is then treated with one molar equivalent of lithium hexamethyldisilazide in dimethylformamide, and the resultant anion is reacted with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 30.8 (Aldrich), to prepare the alkylated product 30.9. The benzyl ester is then converted into the carboxylic acid 30.10, by hydrogenolysis over a palladium catalyst, as described in Org. React., VII, 263, 1953.

Using the above procedures, but employing, in place of the valine derivative 30.6, different aminoacid derivatives 30.1, and/or different bromo-substituted alkyl phosphonates 30.3, the corresponding products 30.5 are obtained.

Scheme 31 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of an alkylene chain and a heteroatom O, S or N. In this procedure, a substituted benzyl alcohol 31.1 is reacted with a dialkyl bromoalkyl phosphonate 31.2 to prepare the ether, thioether or amine product 31.3. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium carbonate, optionally in the presence of a catalytic amount of potassium iodide. The benzyl alcohol product 31.3 is then transformed into a formyl derivative 31.4, in which Lv is a leaving group, as described above (Scheme 22). The formate derivative 31.4 is then reacted with a carboxy-protected amino acid 31.5, using the procedures described above for the preparation of carbamates (Scheme 22), to afford the carbamate product 31.6. The carboxy-protecting group is then removed to afford the carboxylic acid 31.7. The carboxyl protecting group present in the aminoacid 31.5 is selected so that the conditions for removal do not cleave the benzyl carbamate moiety in the substrate 31.6.

For example, 3-methylaminobenzyl alcohol 31.8 is reacted in dimethylformamide solution at ca 70° with one molar equivalent of a dialkyl bromoethyl phosphonate 31.9(Aldrich) and

potassium carbonate, to afford the amine 31.10. The product is then with reacted one molar equivalent of carbonyldiimidazole in tetrahydrofuran, to give the imidazolide product 31.11. The compound is then reacted with the tert. butyl ester of valine 31.12, in pyridine at ambient temperature, to afford the carbamate product 31.13. The tert. butyl ester is then removed by
5 treatment of the ester 31.13 with trifluoroacetic acid at 0°, as described in J. Am. Chem. Soc., 99, 2353, 1977, to afford the carboxylic acid 31.14.

Using the above procedures, but employing, in place of the benzyl alcohol derivative 31.8, different benzyl alcohols 31.1, and/or different bromo-substituted alkyl phosphonates 31.2, the corresponding products 31.7 are obtained.

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Scheme 32 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted benzyl alcohol 32.1 is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate 32.2. The
15 coupled product 32.3 is then converted into the carbamate derivative 32.5, by means of the series of reactions illustrated above (Scheme 31) for the conversion of the benzyl alcohol 31.3 into the carbamate derivative 31.7. Alternatively, the unsaturated compound 32.3 is reduced, diimide or diborane, as described in Comprehensive Organic Transformations, by R. C.

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Larock, VCH, 1989, p.8, to produce the saturated analog 32.4. This material as then transformed, as described above, into the carbamate derivative 32.6.

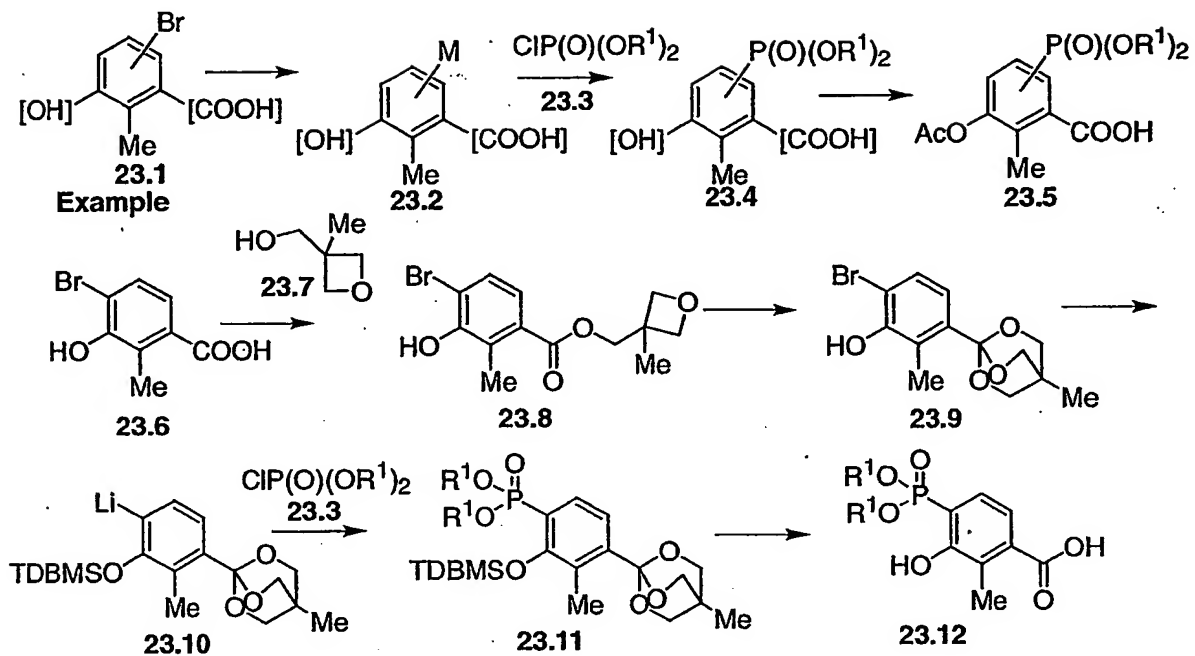
For example, 4-bromobenzyl alcohol 32.7 is coupled, in the presence of diethyl vinylphosphonate, prepared as described in Synthesis, 1983, 556, in the presence of ca. 3 mol % of palladium(II) acetate, triethylamine and tri(o-tolyl)phosphine in acetonitrile at ca. 100°
25 in a sealed tube, as described in Synthesis, 1983, 556, to produce the coupled product 32.9. The product is then converted, as described above, into the unsaturated and saturated carbamate derivatives 32.10 and 32.11.

Using the above procedures, but employing, in place of 4-bromobenzyl alcohol 32.7, different benzyl alcohols 32.1, and/or different dialkyl alkenyl phosphonates 32.2, the corresponding
30 products 32.5 and 32.6 are obtained.

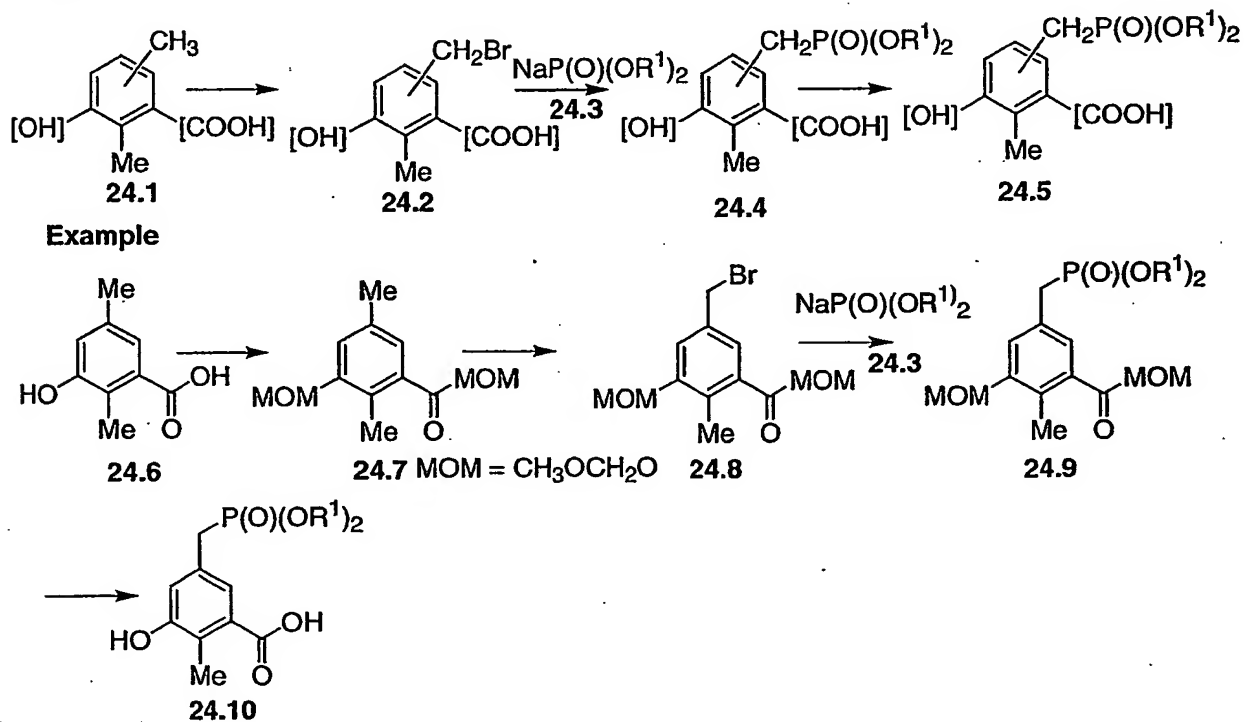
Scheme 33 illustrates the preparation of phosphonate-containing derivatives of the carboxylic acid C4 (Chart 2a) in which the phosphonate group is attached by means of a phenyl ring. In this procedure, a benzaldehyde boronic acid 33.1 is coupled, using the procedures described above (Scheme 27) with a dialkyl bromophenylphosphonate 33.2, to afford the biphenyl derivative 33.3. The aldehyde group is then reduced to give the corresponding benzyl alcohol 33.4. The reduction of aldehydes to afford alcohols is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968. The conversion can be effected by the use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diborane and the like. Preferably, the aldehyde 33.3 is reduced to the carbinol 33.4 by reaction with sodium borohydride in ethanol at ambient temperature. The resulting benzyl alcohol is then transformed, using the procedures described above, (Scheme 31) into the carbamate derivative 33.5.

For example, 3-formylphenylboronic acid 33.6 (Fluka) is coupled with a dialkyl 4-bromophenylphosphonate 33.7, prepared as described in J. Organomet. Chem., 1999, 581, 62, in the presence of tetrakis(triphenylphosphine)palladium and sodium bicarbonate, as described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218, to yield the diphenyl compound 33.8. The aldehyde group is reduced to afford the carbinol 33.9, and the latter compound is then transformed, as described above, into the carbamate derivative 33.10. Using the above procedures, but employing, in place of the benzaldehyde 33.6, different benzaldehydes 33.1, and/or different dialkyl bromophenyl phosphonates 33.2, the corresponding products 33.4 are obtained.

Scheme 23
Method

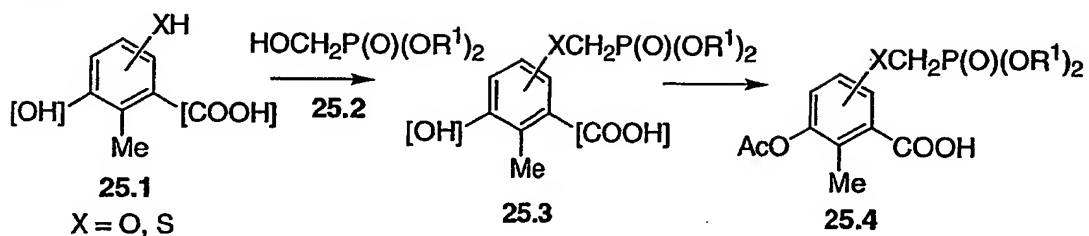


Scheme 24
Method

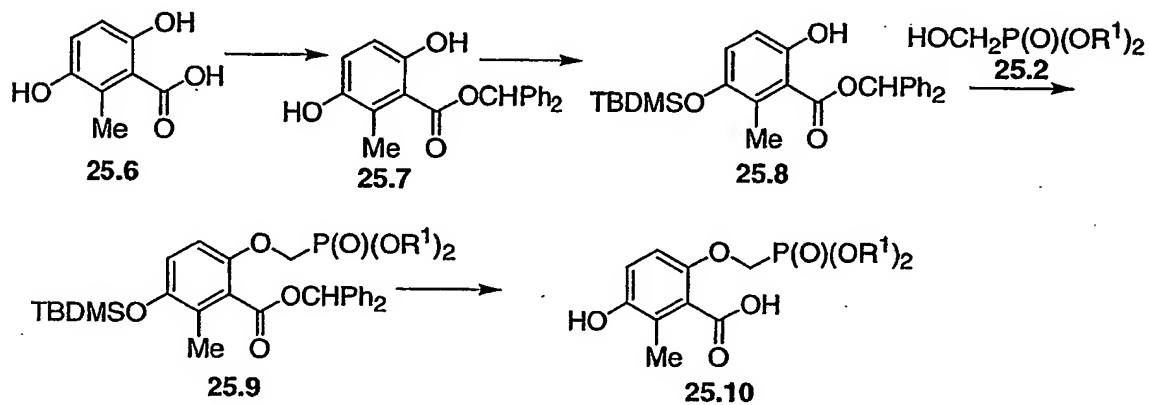


Scheme 25

Method

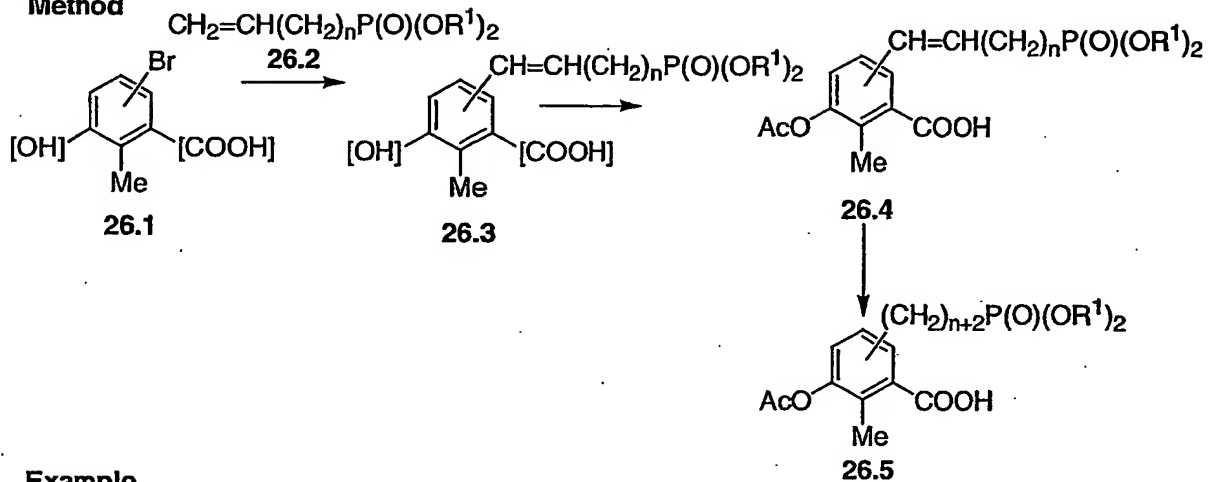


Example

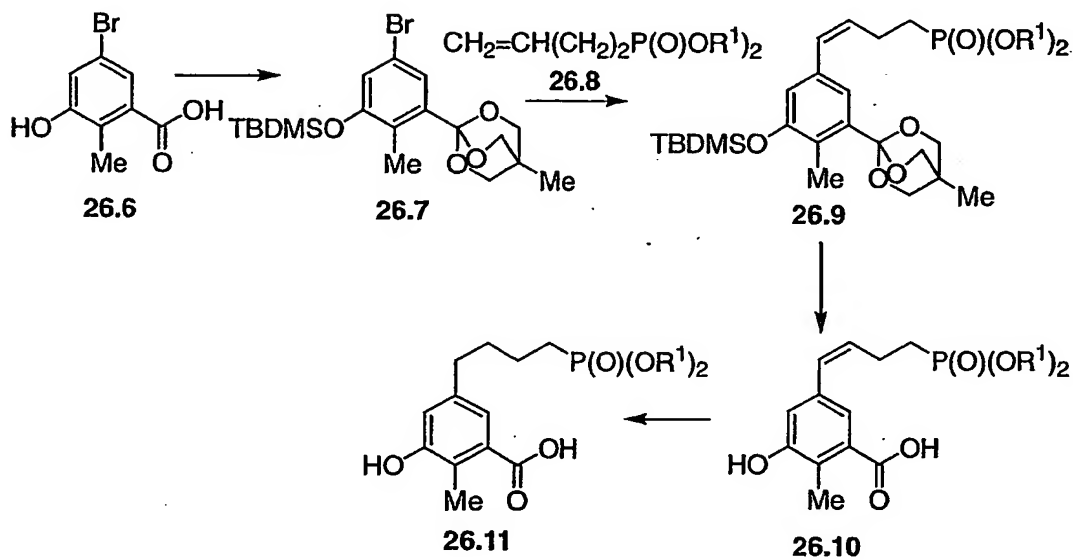


Scheme 26

Method

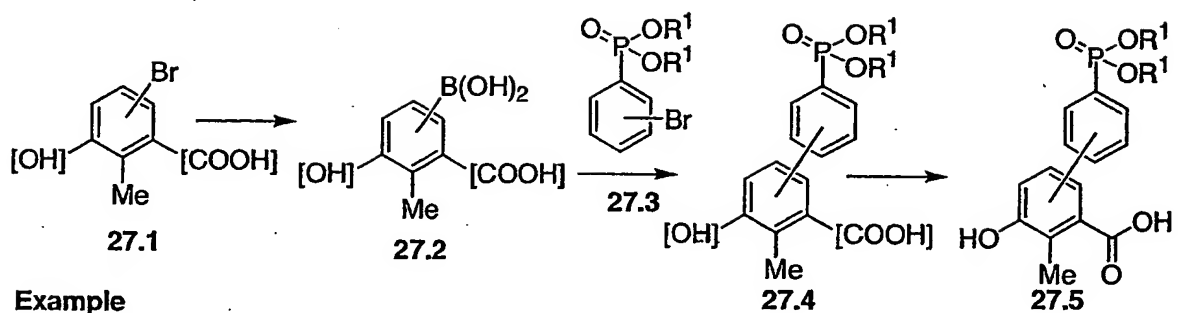


Example

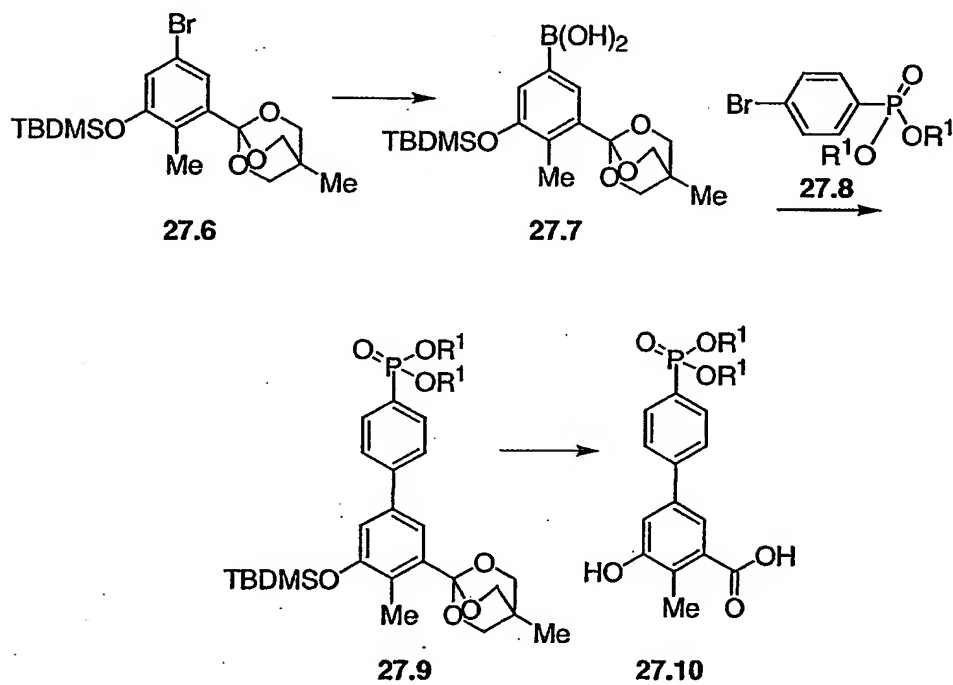


Scheme 27

Method

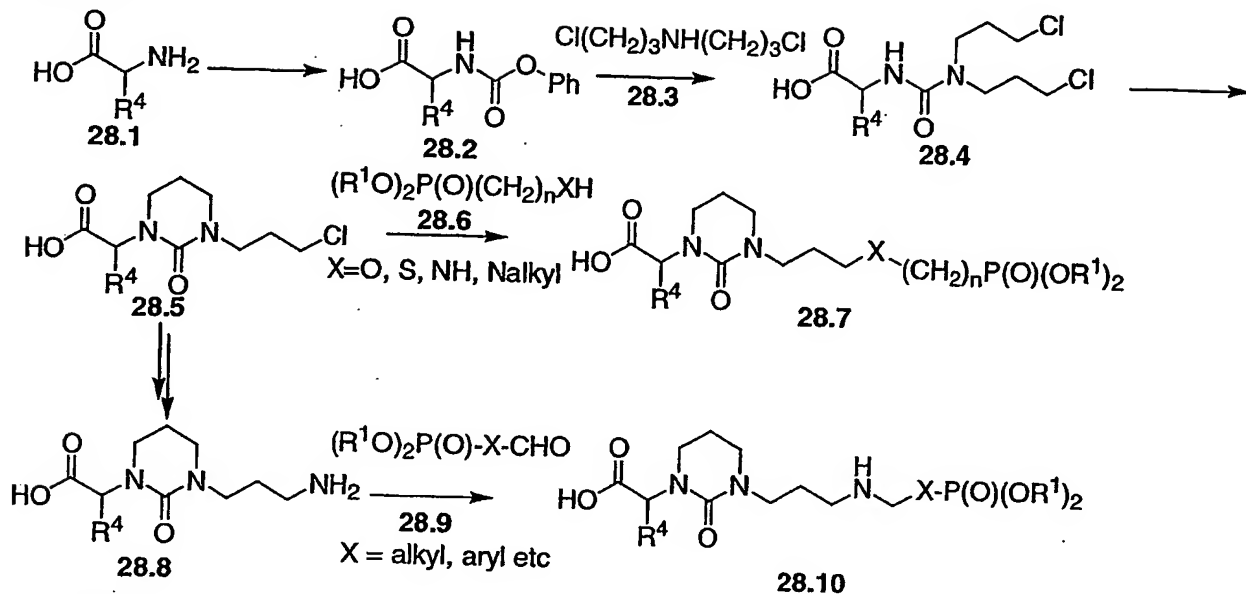


Example

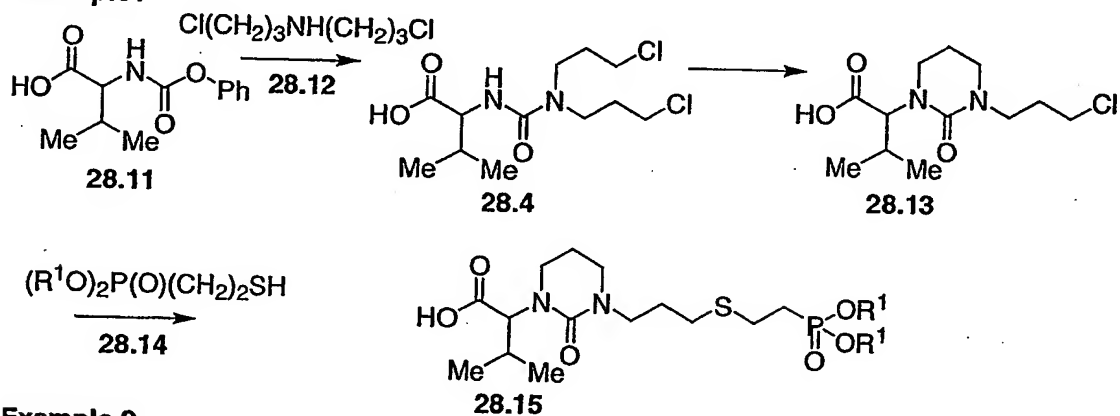


Scheme 28

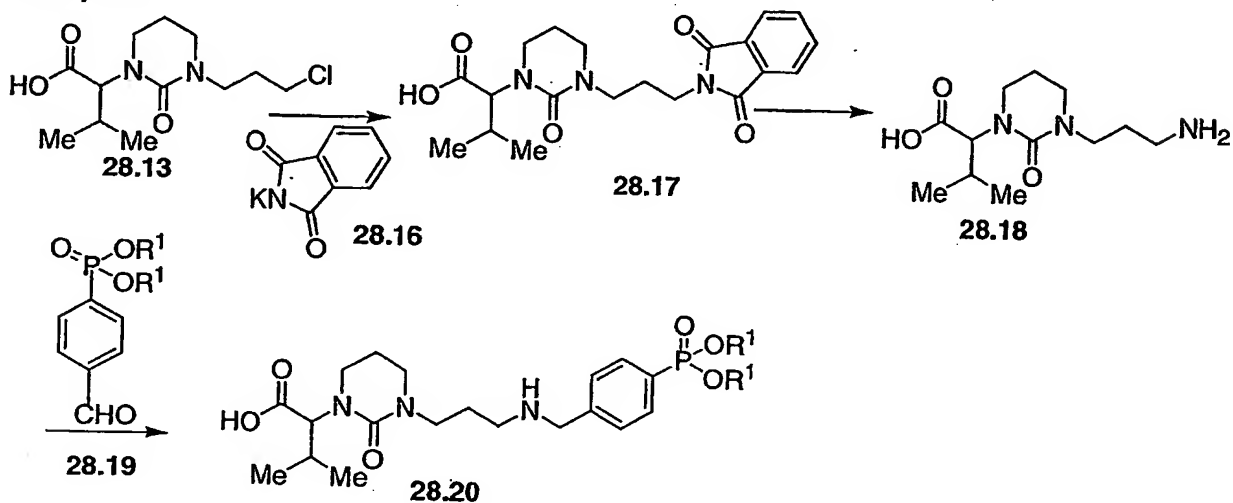
Method



Example1

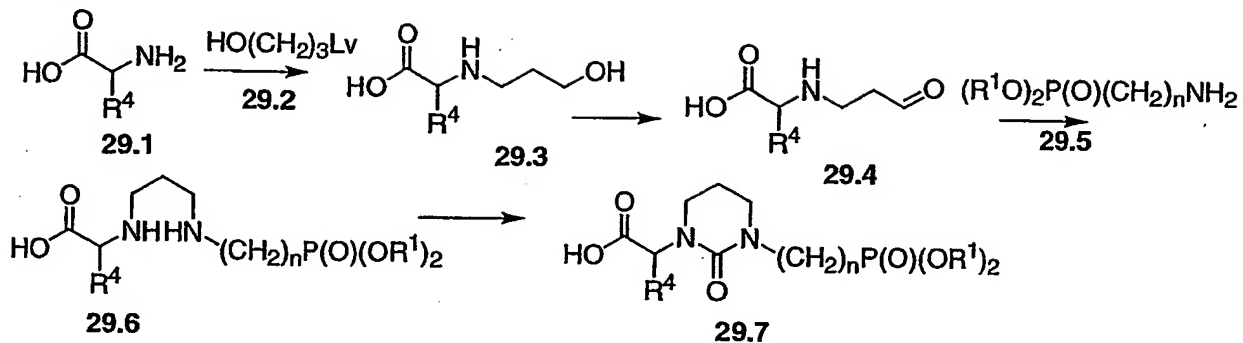


Example 2

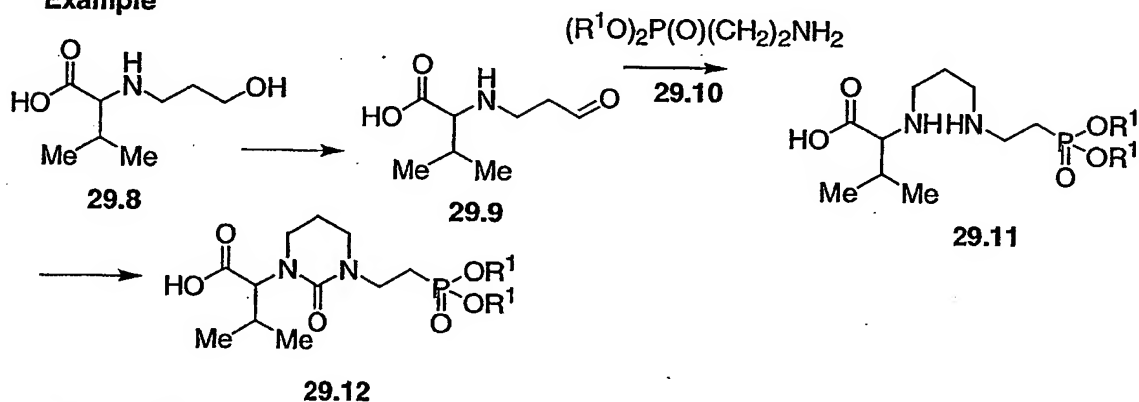


Scheme 29

Method

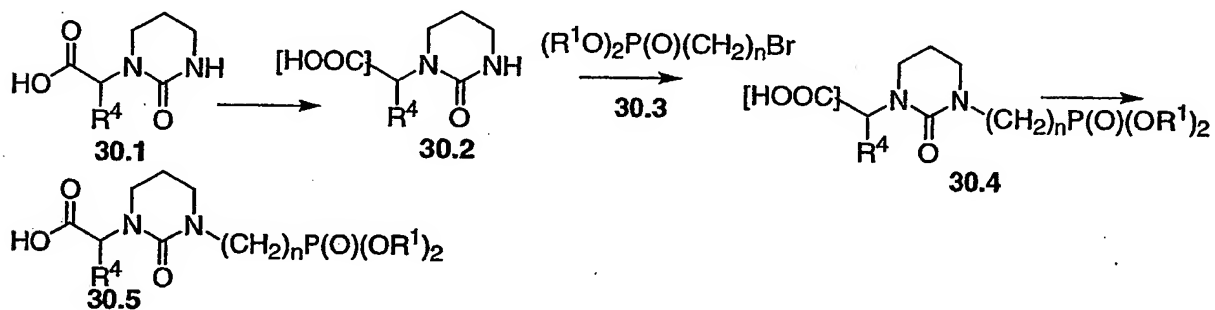


Example

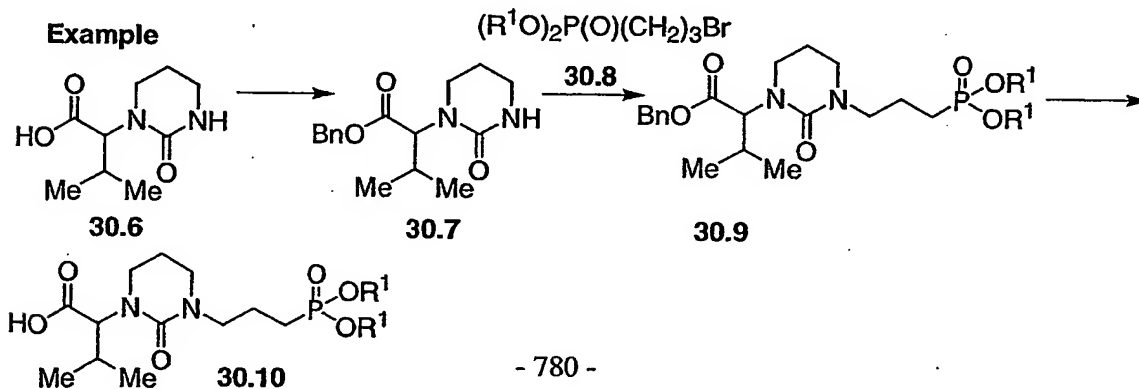


Scheme 30

Method

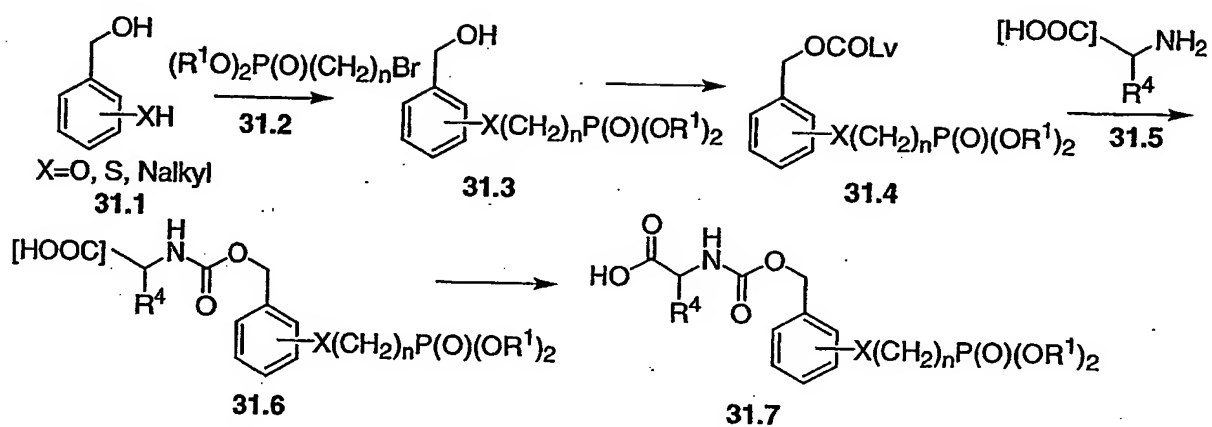


Example

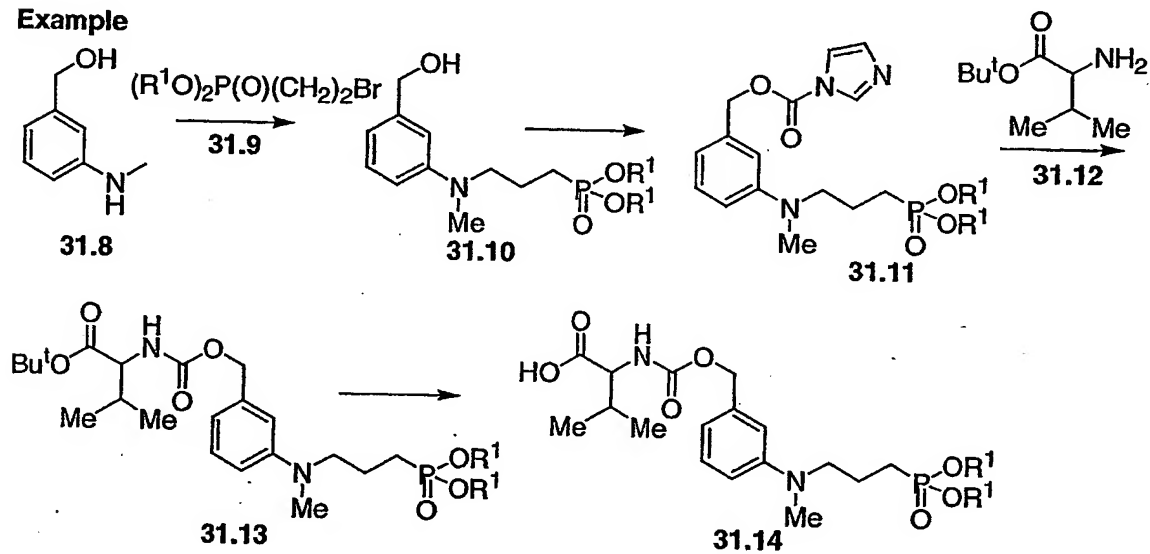


Scheme 31

Method

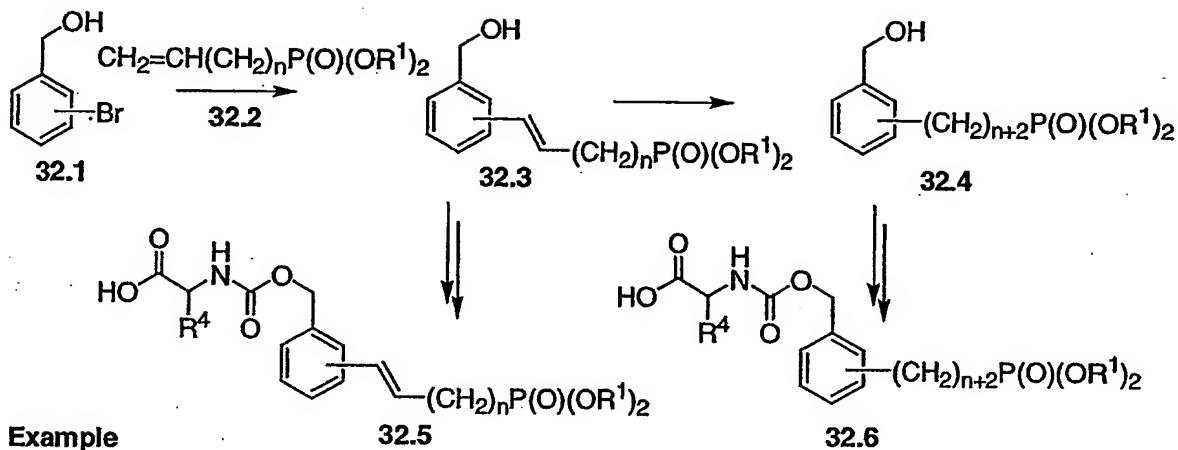


Example

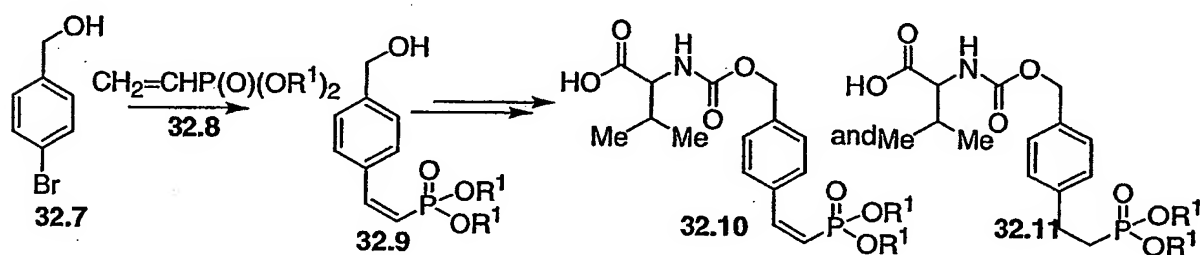


Scheme 32

Method

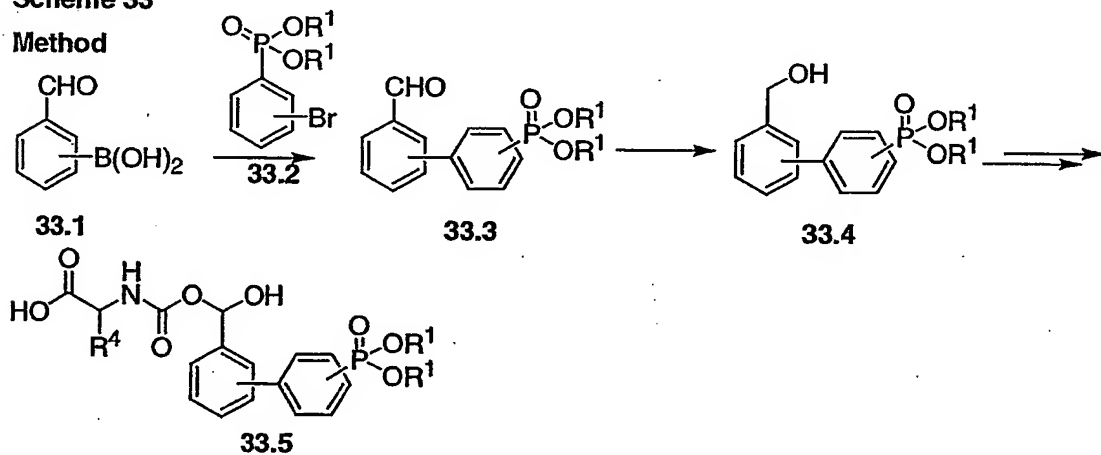


Example

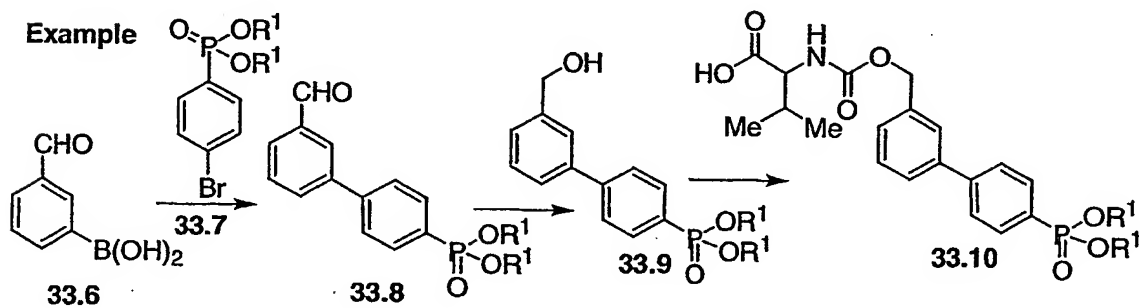


Scheme 33

Method



Example



General applicability of methods for introduction of phosphonate substituents.

The methods described herein for the preparation of phosphonate ester intermediate compounds are, with appropriate modifications, generally applicable to different substrates, such as the carboxylic acids depicted in Charts 2a, 2b and 2c. Thus, the methods described above for the introduction of phosphonate groups into the dimethylphenoxyacetic acid moiety (Schemes 9-14), can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the phenylalanine synthon for the preparation of the phosphonate esters 3. Similarly, the methods described above for the introduction of phosphonate groups into the phenylalanine moiety (Schemes 15-17), the hydroxy methyl substituted benzoic acids (Schemes 23- 27), the tetrahydropyrimidine analogs (Schemes 28-30), and the benzyl carbamates (Schemes 31- 33) can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate groups into the dimethylphenoxyacetic acid component.

Atazanavir-like phosphonate protease inhibitors (ATLPPD)

Preparation of the intermediate phosphonate esters.

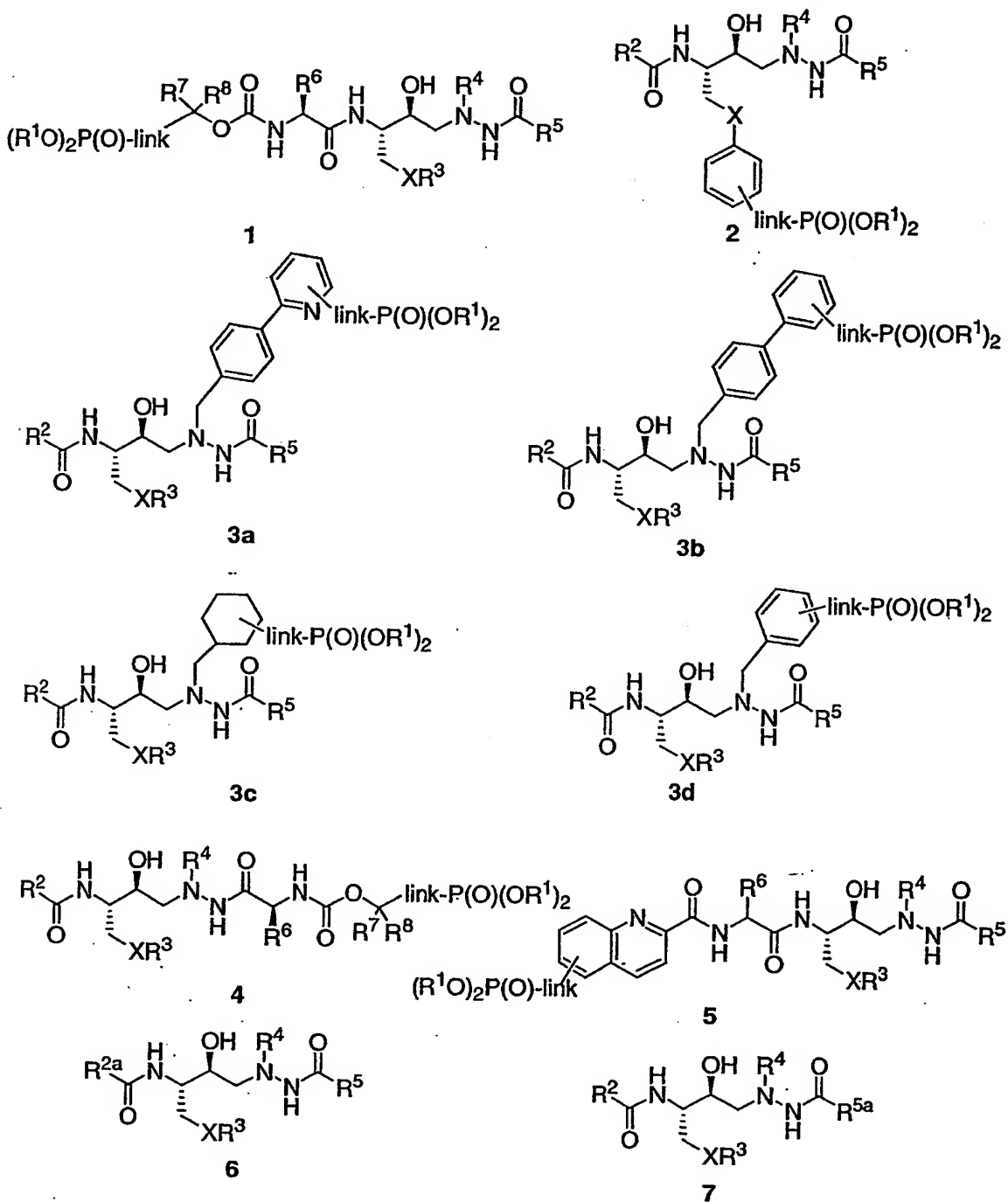
The structures of the intermediate phosphonate esters 1 to 7, and the structures for the component groups X, R¹, R⁷ and R⁸ of this invention are shown in Chart 1. The structures of the R²COOH and R⁵COOH components are shown in Charts 2a, 2b and 2c, and the structures of the R³XCH₂ components are shown in Chart 3. The structures of the R⁴ components are shown in Chart 4. Specific stereoisomers of some of the structures are shown in Charts 1-4; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 7. Subsequent chemical modifications to the compounds 1 to 7, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds 1 to 7 incorporate a phosphonate moiety (R¹O)₂P(O) connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 5 and 6 illustrate examples of the linking groups present in the structures 1 - 7. The term "etc" in Charts 3, 5 and 6, refers to the scaffold atazanavir.

Schemes 1 - 56 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1- 5, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 6 and 7, in which the phosphonate moiety is incorporated into the groups R^2COOH and R^5COOH , are also described below.

5

Chart 1. Structures of the phosphonate esters 1 - 7.



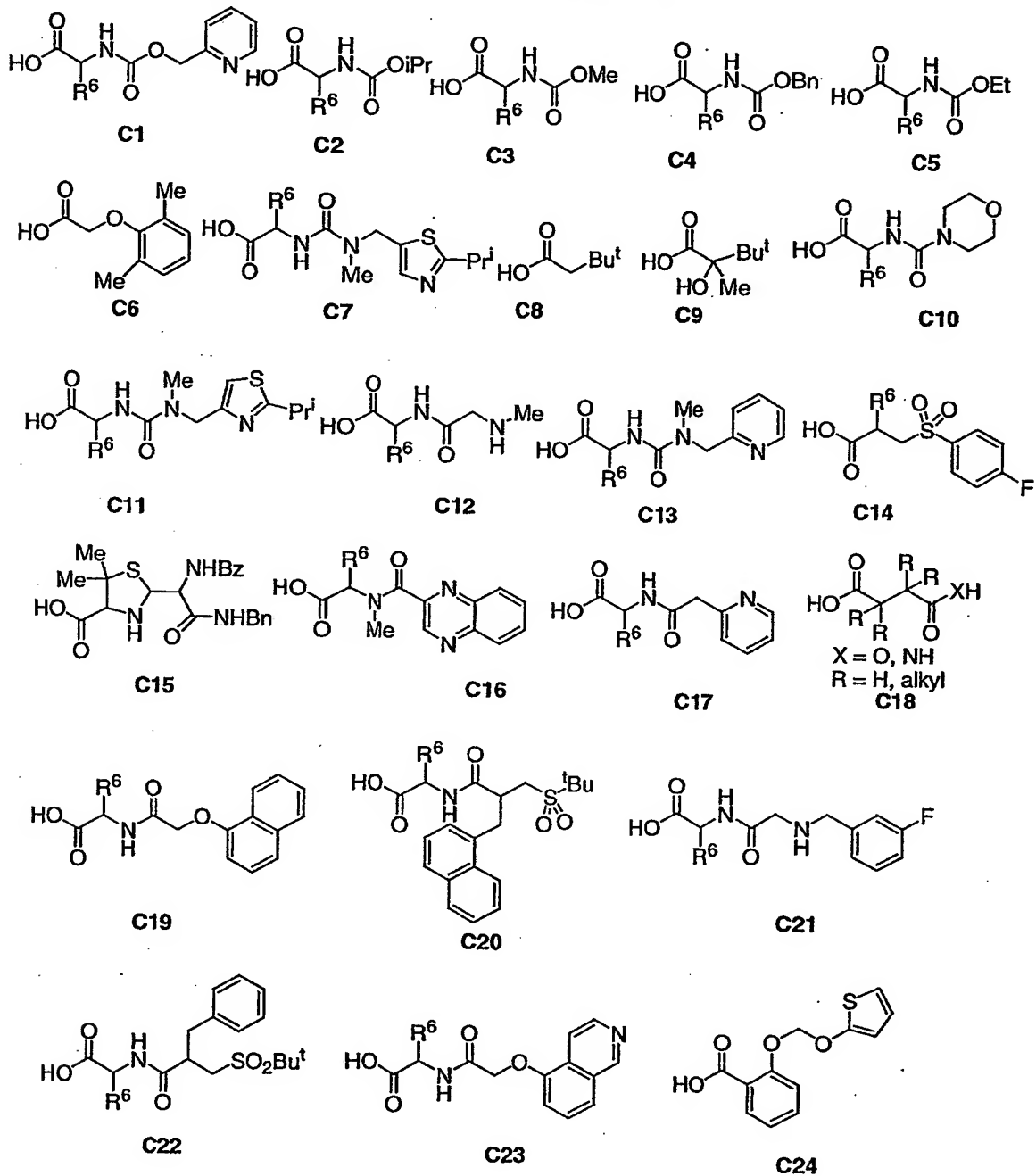
R^{2a} = phosphonate-containing R^2

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

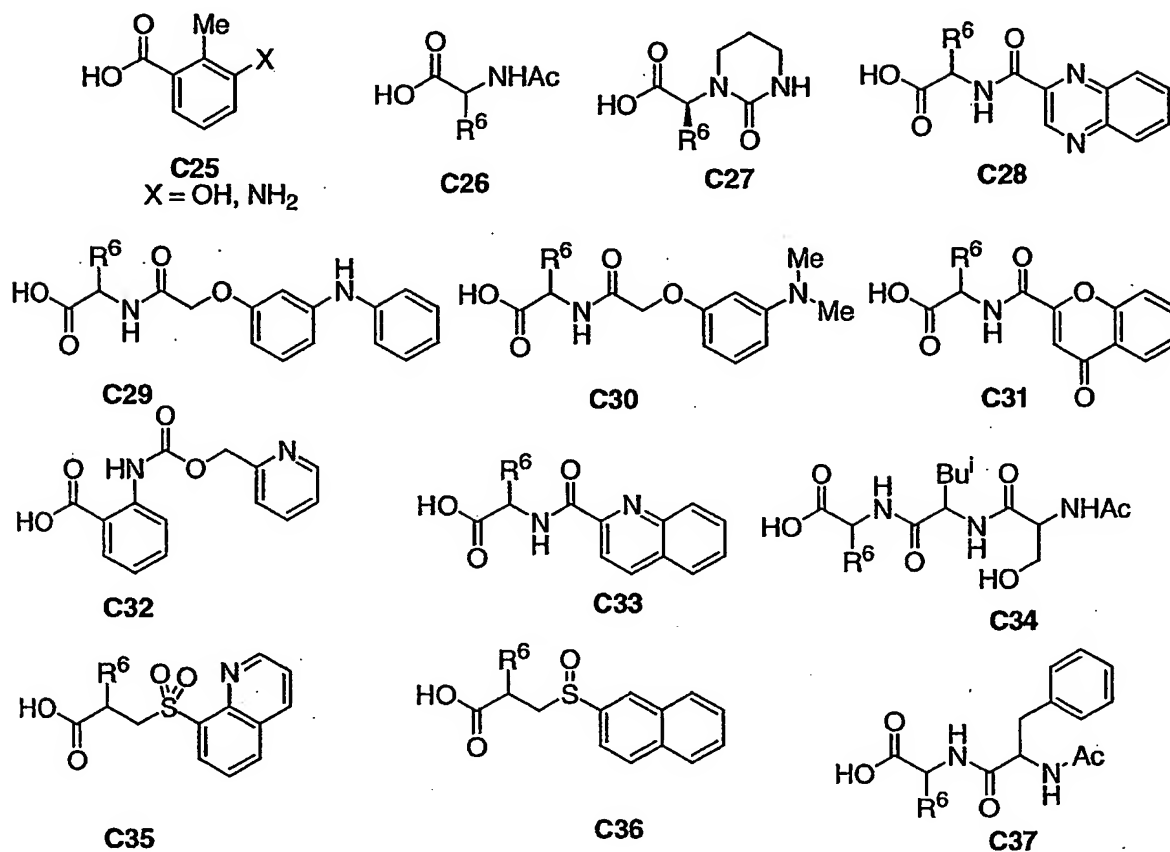
R^7, R^8 = H, alkyl

X = direct bond; sulfur.

R^{5a} = phosphonate-containing R^5

Chart 2a Structures of the R²COOH and R⁵COOH components

R⁶ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl,
 CH₂NHAc, CH₂NHCOCF₃

Chart 2b Structures of the R²COOH and R⁵COOH components

R⁶ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, NHAc, NHCOCF₃

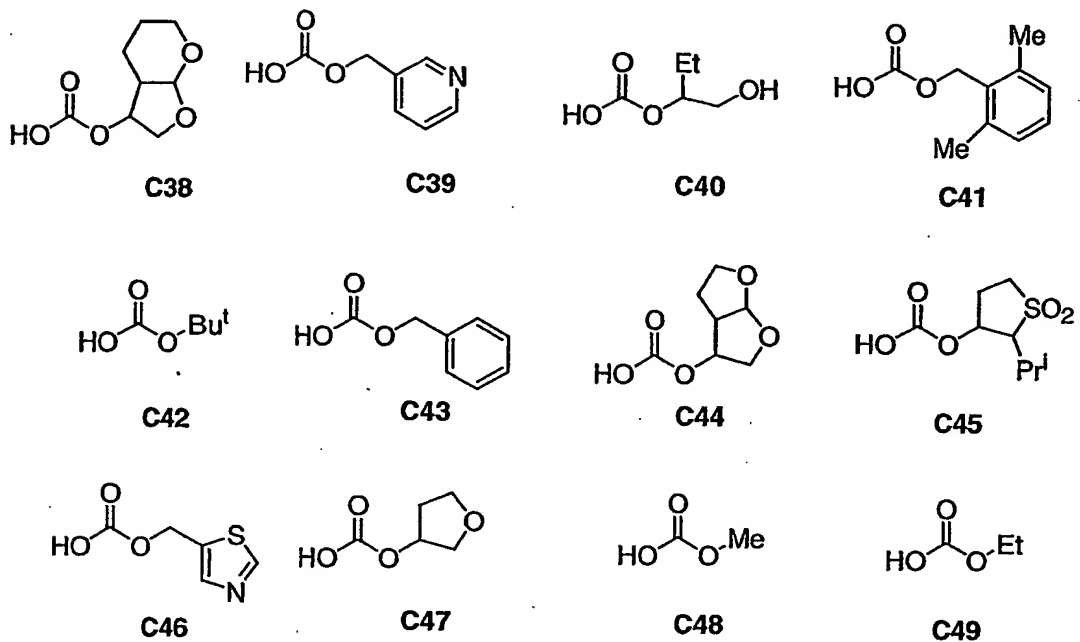
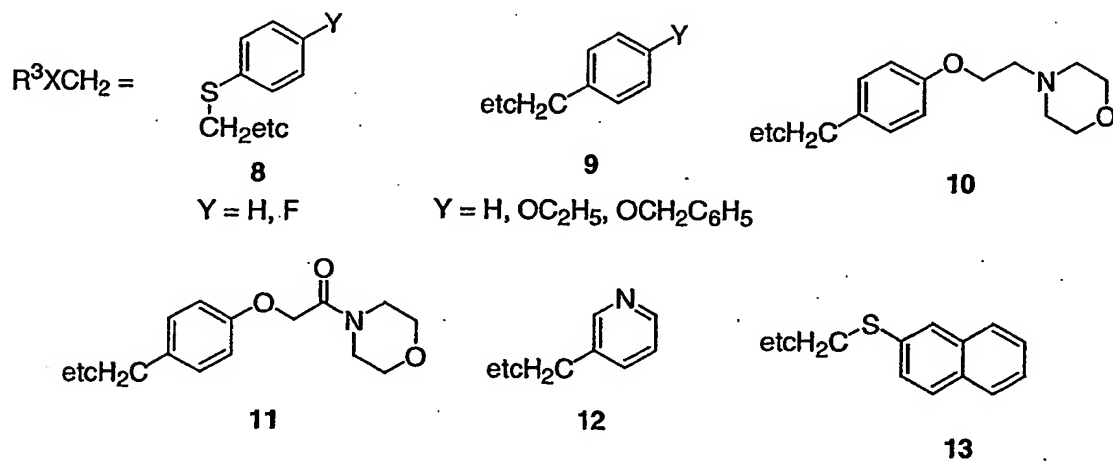
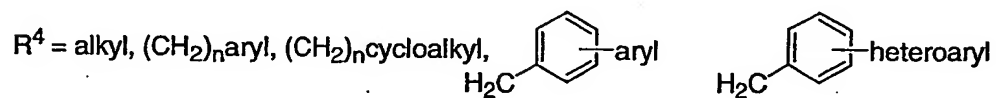
Chart 2c Structures of the $R^2\text{COOH}$ and $R^5\text{COOH}$ componentsChart 3 Structures of the $R^3\text{XCH}_2$ groups.Chart 4 Structures of the R^4 groups

Chart 5 Examples of the linking group between the scaffold and the phosphonate moiety.

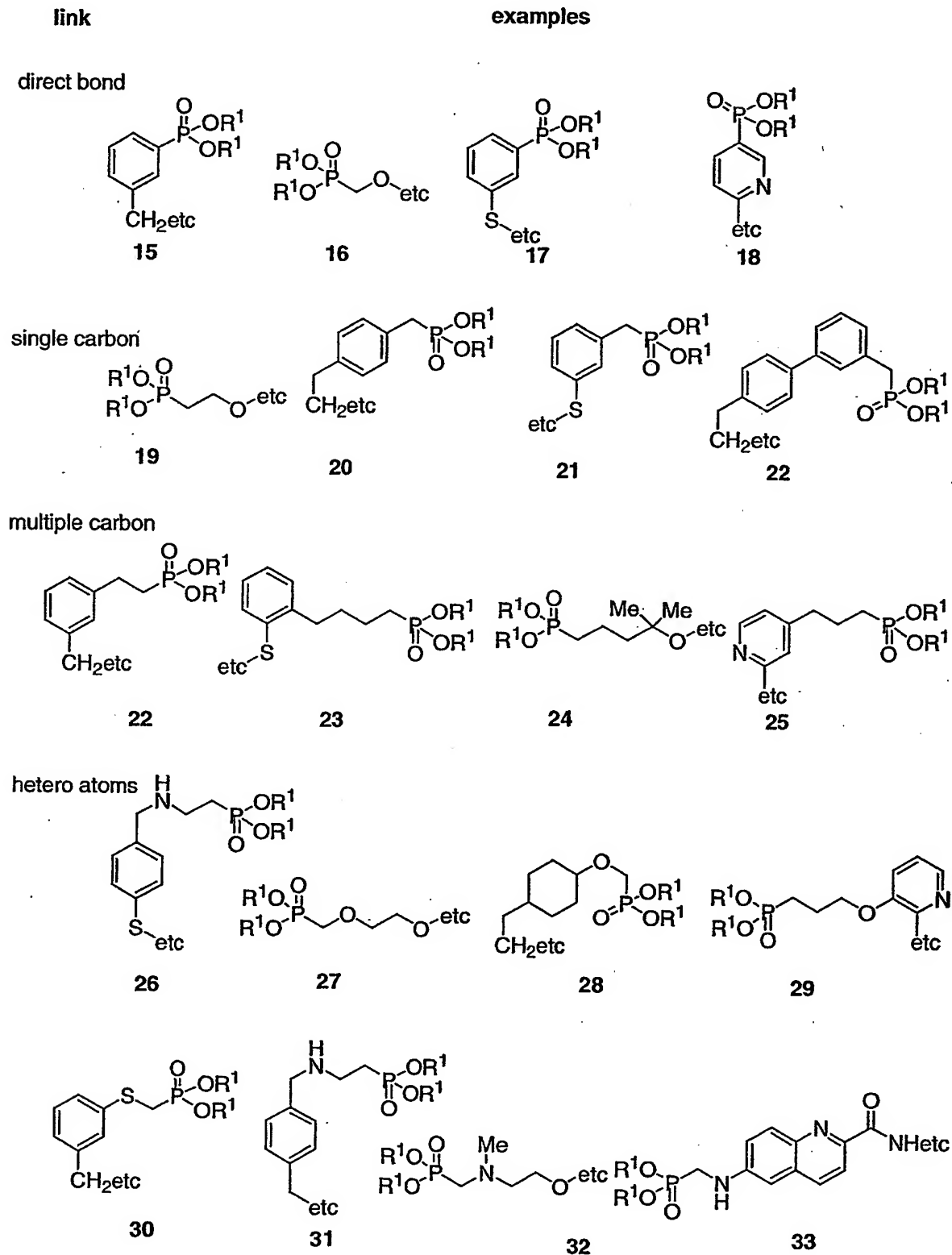
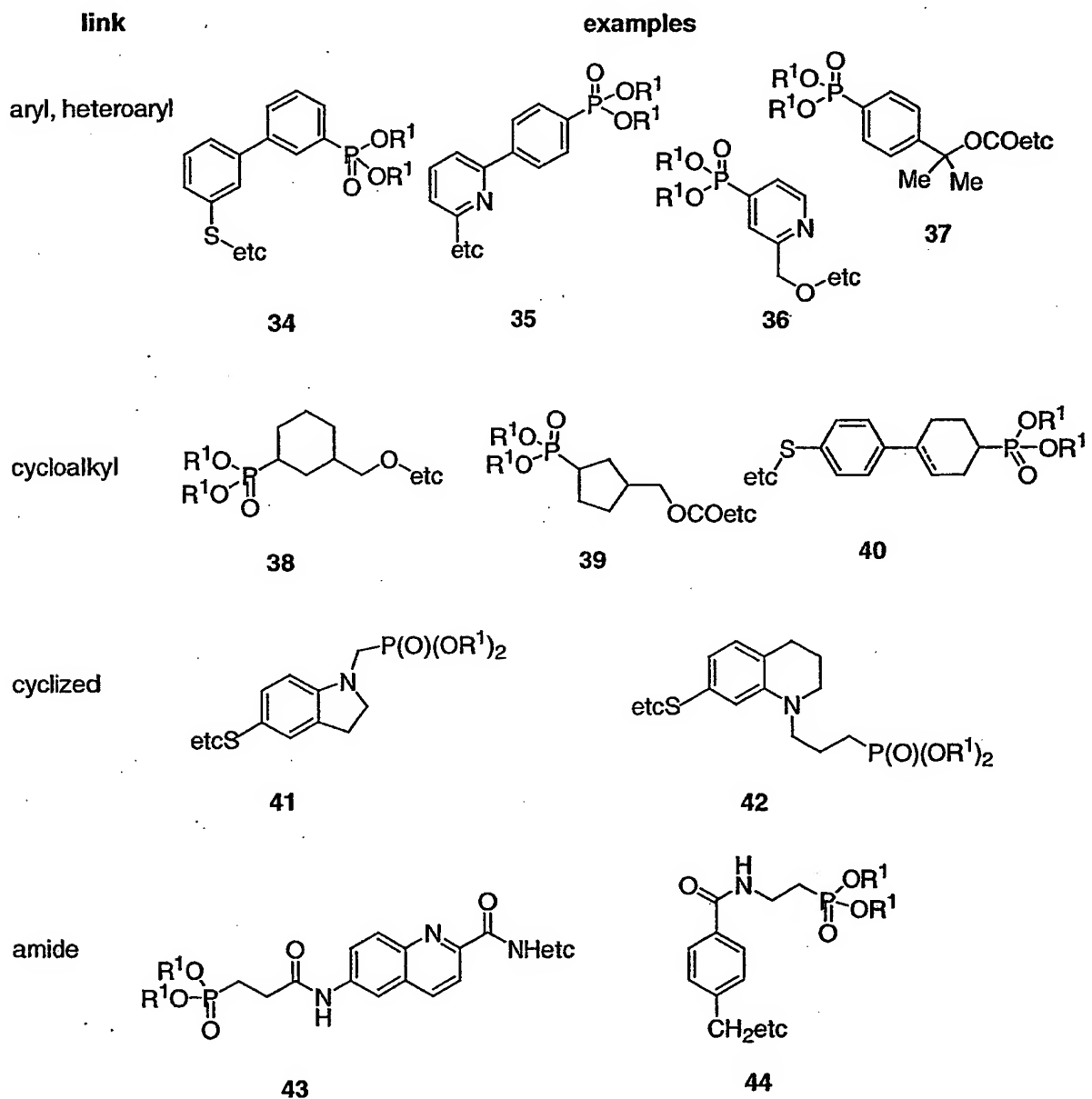


Chart 6 Examples of the linking group between the scaffold and the phosphonate moiety.



Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain
5 reactive substituents from unwanted reactions by protection before the sequence described,
and to deprotect the substituents afterwards, according to the knowledge of one skilled in the
art. Protection and deprotection of functional groups are described, for example, in *Protective
Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990.
Reactive substituents which may be protected are shown in the accompanying schemes as, for
10 example, [OH], [SH].

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes 1 and 2 illustrate the preparation of the phosphonate esters 1 in which X is a direct
15 bond. As shown in Scheme 1, the oxirane 1.1 is reacted with the BOC-protected hydrazine
derivative 1.2 to afford the aminoalcohol 1.3. The preparation of the oxiranes 1.1, in which Y
is as defined in Scheme 1, is described below, (Scheme 3). The preparation of the hydrazine
derivatives $R^4NHNHBOC$ is described below, (Scheme 4). The reaction between the oxirane
1.1 and the hydrazine 1.2 is conducted in a polar organic solvent such as dimethylformamide,
20 acetonitrile or, preferably, a lower alkanol. For example, equimolar amounts of the reactants
are combined in isopropanol and heated to ca. 80° for about 16 hours, as described in WO
9740029, to afford the aminoalcohol 1.3. The cbz protecting group is then removed from the
product to yield the free amine 1.4. The removal of carbobenzyloxy substituents to afford the
corresponding amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene
25 and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the
use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a
palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate
with triethylsilane, triethylamine and a catalytic amount of palladium (II) chloride, as described
in *Chem. Ber.*, 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient
30 temperature, as described in *J. Chem. Soc., Perkin Trans. I*, 1277, 1988. The cbz group can
also be removed by treatment with a Lewis acid such as boron tribromide, as described in *J.
Org. Chem.*, 39, 1247, 1974, or aluminum chloride, as described in *Tet. Lett.*, 2793, 1979.

Preferably, the protected amine 1.3 is converted into the free amine 1.4 by means of hydrogenation over 10% palladium on carbon catalyst in ethanol, as described in US Patent 5196438.

5 The amine product 1.4 is then reacted with a carboxylic acid 1.5 to afford the amide 1.6. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the
10 presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, imidazolide and the like, and then reacted with the amine, in the presence of
15 an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane. Preferably, equimolar amounts of the amine and the carboxylic acid are reacted in tetrahydrofuran at ca. -10° , in the presence
20 of dicyclohexylcarbodiimide, as described in U.S. Patent 5,196,438, to afford the aminoamide 1.6. The aminoamide is then reacted with a reagent $A-CR^7R^8OCOX$ (1.7), in which the substituent A is the group $(R^1O)_2P(O)$ -link, or a precursor group thereto, such as $[OH]$, $[SH]$, $[NH]$, Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate 1.8. The reagent $A-CR^7R^8OCOX$ is derived from the corresponding alcohol A-
25 CR^7R^8OH , using methods described below, (Scheme 20). The preparation of the reactants A- CR^7R^8OCOX is described in Schemes 21 - 26. The preparation of carbamates by means of reactions between alcohols and amines is described in Scheme 20.

The BOC-protected amine present in the carbamate product 1.8 is then deprotected to produce the free amine 1.9. The removal of BOC protecting groups is described, for example,
30 in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid or formic acid, or

by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC group is removed by treatment of the substrate **1.8** with hydrogen chloride in tetrahydrofuran, for example as described in *Org. Process Res. Dev.*, 2002, 6, 323. The resulting amine **1.9** is then coupled with a carboxylic acid or an activated derivative thereof **1.10**, to afford the amide

5 **1.11**, using the conditions described above for the preparation of the amide **1.6**.

For example, the amine **1.9** is reacted with the carboxylic acid **1.10**, $X = OH$, in the presence of a water-soluble carbodiimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydroxybenztriazole and triethylamine, as described in *J. Med. Chem.*, 41, 1988, 3387, to yield the amide **1.11**.

10 The procedures illustrated in Scheme 1 depict the preparation of the compounds **1.11** in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as $[OH]$, $[SH]$, Br, as described below. Scheme 2 illustrates the conversion of compounds **1.11** in which A is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds **1**. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1\text{)}_2$ are illustrated below,

15 (Schemes 21 - 56). In the procedures illustrated above, (Scheme 1) and in the procedures illustrated below (Schemes 3 - 19) for the preparation of the phosphonate esters **1 - 7**, compounds in which the group A is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$ may be converted into compounds in which A is $\text{link-P(O)(OR}^1\text{)}_2$ at any appropriate stage in the reaction sequence, or, as shown in Scheme 2, at the end of the sequence. The selection of an

20 appropriate stage to effect the conversion of the group A into the group $\text{link-P(O)(OR}^1\text{)}_2$ is made after consideration of the nature of the reactions involved in the conversion, and the stability of the various components of the substrate to those reaction conditions.

Scheme 3 illustrates the preparation of the epoxides **1.1** used above in Scheme 1. The

25 preparation of the epoxide **1.1** in which R^7 is H is described in *J. Org. Chem.*, 1994, 59, 3656. Analogs in which R^7 is one of the substituents defined in Chart 3 are prepared as shown in Scheme 3. A substituted phenylalanine **3.1** is first converted into the benzyloxycarbonyl (cbz) derivative **3.2**. The preparation of benzyloxycarbonyl amines is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990,

30 p. 335. The aminoacid **3.1** is reacted with benzyl chloroformate or dibenzyl carbonate in the presence of a suitable base such as sodium carbonate or triethylamine, to afford the protected amine product **3.2**. The conversion of the carboxylic acid **3.2** into the epoxide **1.1**, for

example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, and in J. Org. Chem., 1994, 59, 3656 is then effected. The carboxylic acid is first converted into an activated derivative such as the acid chloride 3.3, in which X is Cl., for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 3.4. The reaction is performed by the addition of a solution of the activated carboxylic acid derivative to an ethereal solution of three or more molar equivalents of diazomethane at 0°. The diazoketone 3.4 is converted into the chloroketone 3.5 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether, as described in J. Org. Chem., 1994, 59, 3656. The latter compound is then reduced, for example by the use of an equimolar amount of sodium borohydride in an ethereal solvent such as tetrahydrofuran at 0°, to produce a mixture of chlorohydrins from which the minor diastereomer 3.6 is separated by chromatography. The chlorohydrin 3.6 is then converted into the epoxide 1.1 by treatment with a base such as an alkali metal hydroxide in an alcoholic solvent, for example as described in J. Med. Chem., 1997, 40, 3979. Preferably, the compound 3.6 is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1. The preparations of analogs of the oxirane 1.1 in which the amino group is protected respectively as the tert-butoxycarbonyl and trifluoroacetyl derivatives are described respectively in J. Med. Chem., 1994, 37, 1758 and J. Med. Chem., 1996, 39, 3203.

Scheme 4 depicts the preparation of the hydrazine derivatives 1.2, in which R⁴ is CH₂-aryl, CH₂-alkyl, CH₂-cycloalkyl as shown in Chart 4. The general procedure for the preparation of BOC-protected hydrazine derivatives from the corresponding aldehyde RCHO (4.1) is shown in Scheme 4. The aldehyde is reacted with tert. butyl carbazate 4.2, in a solvent such as an alkanol, a hydrocarbon such as toluene, or a polar organic solvent such as dimethylformamide, to afford the substituted hydrazone 4.3. Preferably, equimolar amounts of the reactants are heated in a mixture of toluene and isopropanol, as described in Org. Process Res. Dev., 2002, 6, 323, to prepare the hydrazone 4.3. The product is then reduced to the corresponding hydrazine derivative 4.4. The transformation can be effected by chemical reduction, for example by the use of sodium borohydride, sodium cyanoborohydride, or sodium triacetoxyborohydride or the like, or by palladium-catalyzed reduction in the presence of hydrogen or a hydrogen donor such as ammonium formate. Preferably, the hydrazone 4.3

is reduced to the hydrazine 4.4 by hydrogenation at ambient temperature and pressure, in the presence of palladium hydroxide on carbon, as described in Org. Process Res. Dev., 2002, 6, 323.

The preparation of the hydrazine derivatives 1.2 in which a diaryl moiety is present is shown in Scheme 4, Example 1. In this procedure, a formyl-substituted phenyl boronate 4.5 (Lancaster Synthesis) is transformed, by means of a palladium-catalyzed coupling with an aryl or heteroaryl bromide 4.6, to afford the aldehyde 4.7. The coupling of aryl bromides with aryl boronates is described, for example, in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218 and in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 57. Typically, the reactants 4.5 and 4.6 are combined in an aprotic organic solvent such as dimethylformamide in the presence of a palladium (0) catalyst such as tetrakis(triphenylphosphine)palladium and a base such as sodium bicarbonate or potassium acetate, to afford the coupled product 4.7. This material is then reacted with a protected hydrazine derivative such as tert-butoxycarbonylhydrazine (tert-butyl carbazate) 4.2, to yield the hydrazone 4.8. The reaction between equimolar amounts of the aldehyde and the protected hydrazine is conducted in alcoholic solvent such as ethanol, at reflux temperature, for example as described in WO9740029, to produce the hydrazone 4.8. The latter compound is then reduced, for example by the use of hydrogen in the presence of a palladium catalyst, as described in WO 9740029, or by the use of sodium cyanoborohydride and p-toluenesulfonic acid in tetrahydrofuran, as described in J. Med. Chem., 1998, 41, 3387, to afford the substituted hydrazine 1.2. Other reactants 1.2, in which R⁴ is as defined in Chart 4, are prepared from the appropriate aldehydes, using the procedures of Scheme 4.

Scheme 4, Example 2 illustrates the preparation of phosphonate-containing pyridylphenyl hydrazine derivatives 4.11, which are employed in the preparation of the phosphonate esters 3a. In this procedure, a phosphonate-substituted pyridyl benzaldehyde 4.9, the preparation of which is described below, (Schemes 40 and 41) is reacted, as described above, with tert. butyl carbazate 4.2, to afford the hydrazone 4.10. This compound is then reduced, in the presence of palladium hydroxide as catalyst, as described above, to yield the hydrazine product 4.11.

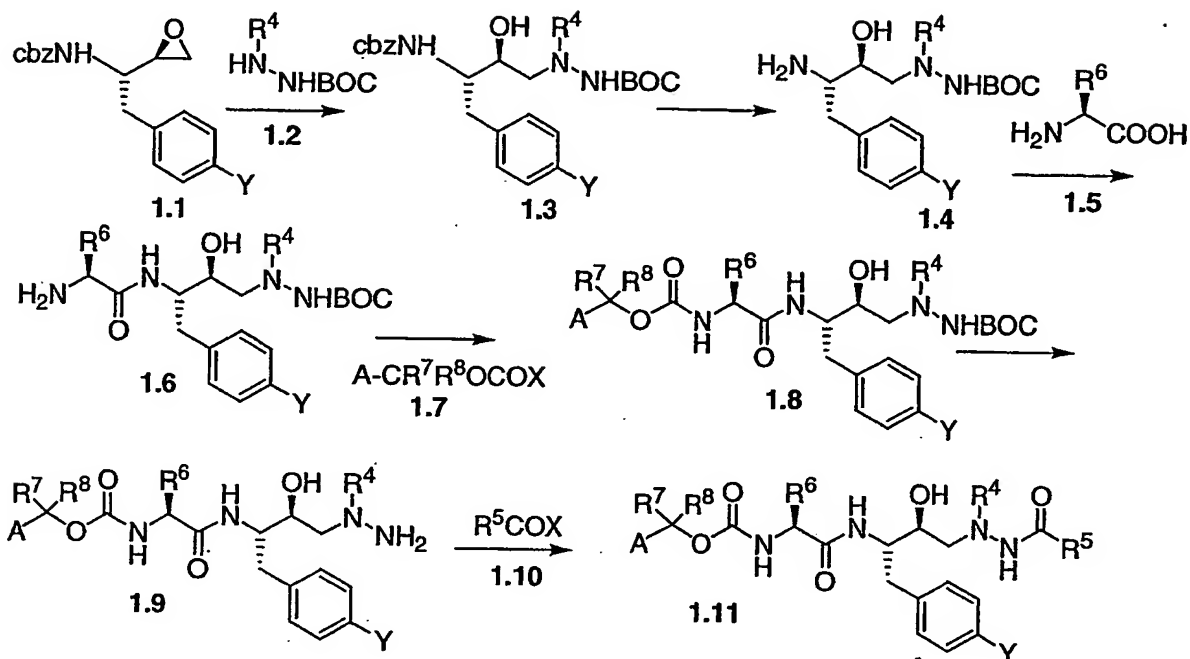
Scheme 4, Example 3 illustrates the preparation of phosphonate-containing biphenyl hydrazine derivatives 4.13, which are employed in the preparation of the phosphonate esters 3b. In this procedure, a phosphonate-substituted phenyl benzaldehyde 4.12 the preparation of which is

described below, (Schemes 42- 44) is converted, as described above in Example 2 into hydrazine product 4.13.

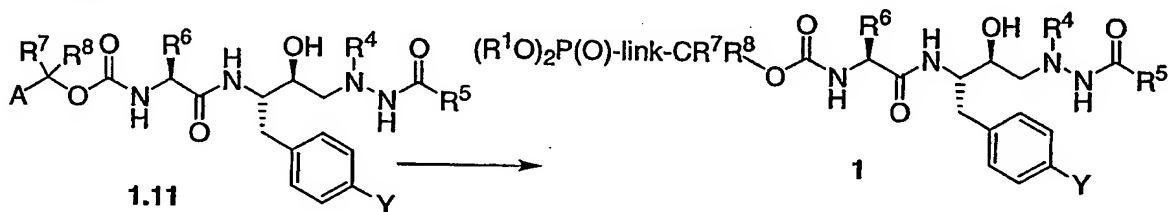
Scheme 4, Example 4 illustrates the preparation of phosphonate-containing phenyl hydrazine derivatives 4.15, which are employed in the preparation of the phosphonate esters 3d. In this
5 procedure, a phosphonate-substituted phenyl benzaldehyde 4.14, the preparation of which is described below, (Schemes 45 - 48) is converted, as described above in Example 2 into hydrazine product 4.15.

Scheme 4, Example 5 illustrates the preparation of phosphonate-containing cyclohexyl hydrazine derivatives 4.17, which are employed in the preparation of the phosphonate esters
10 3c. In this procedure, a phosphonate-substituted cyclohexane carboxaldehyde 4.16, the preparation of which is described below, (Schemes 49 - 52) is converted, as described above in Example 2 into hydrazine product 4.17.

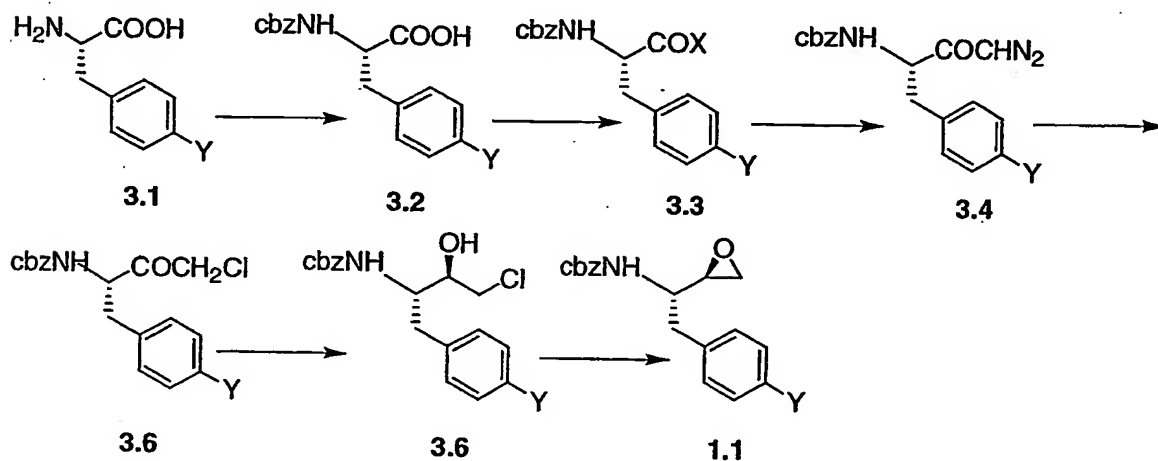
Scheme 1



Scheme 2



Scheme 3

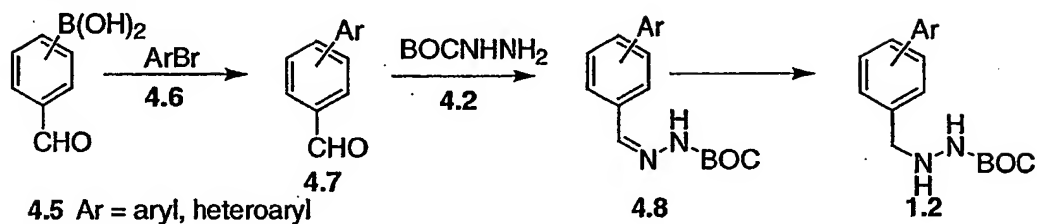


Scheme 4

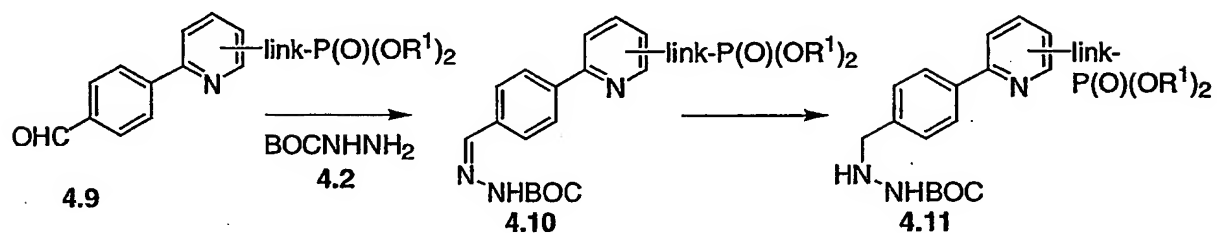
General reaction



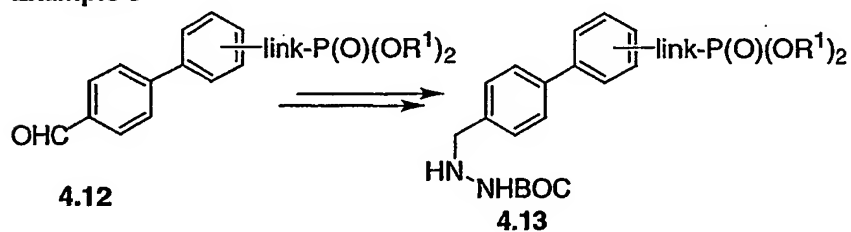
Example 1



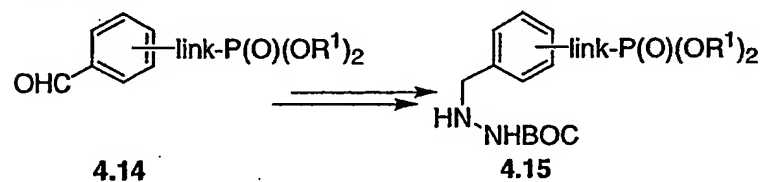
Example 2



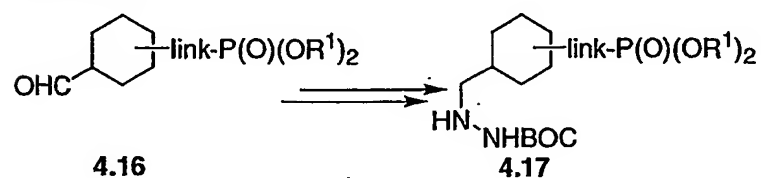
Example 3



Example 4



Example 5



Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes 5 and 6 illustrate the preparation of the compounds 1 in which X is sulfur. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 5.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol R^3SH 5.2, as defined above, to afford the thioether 5.3.

The reaction is conducted in an organic solvent such as, for example, pyridine, DMF, toluene and the like, optionally in the presence of water, in the presence of an inorganic or organic base, at from 0° to 80°, for from 1-12 hours. Preferably the mesylate 5.1 is reacted with an equimolar amount of the thiol R^3SH 5.2, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°, as described in J. Org. Chem., 1994, 59, 3656, to give the product 5.3. The 1,3-dioxolane protecting group present in the compound 5.3 is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol 5.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 5.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 5.3 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°, to yield the diol product 5.4.

The primary hydroxyl group of the diol 5.4 is then selectively activated by reaction with an electron-withdrawing reagent such as, for example, dinitrobenzoyl chloride or p-toluenesulfonyl chloride. The reaction is conducted in an inert solvent such as pyridine, dichloromethane and the like, in the presence of an inorganic or organic base.

Preferably, equimolar amounts of the diol 5.4 and p-toluenesulfonyl chloride are reacted in a solvent such as pyridine, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, as described in J. Org. Chem, 2000, 65, 1623, to afford the p-toluenesulfonate ester 5.5.

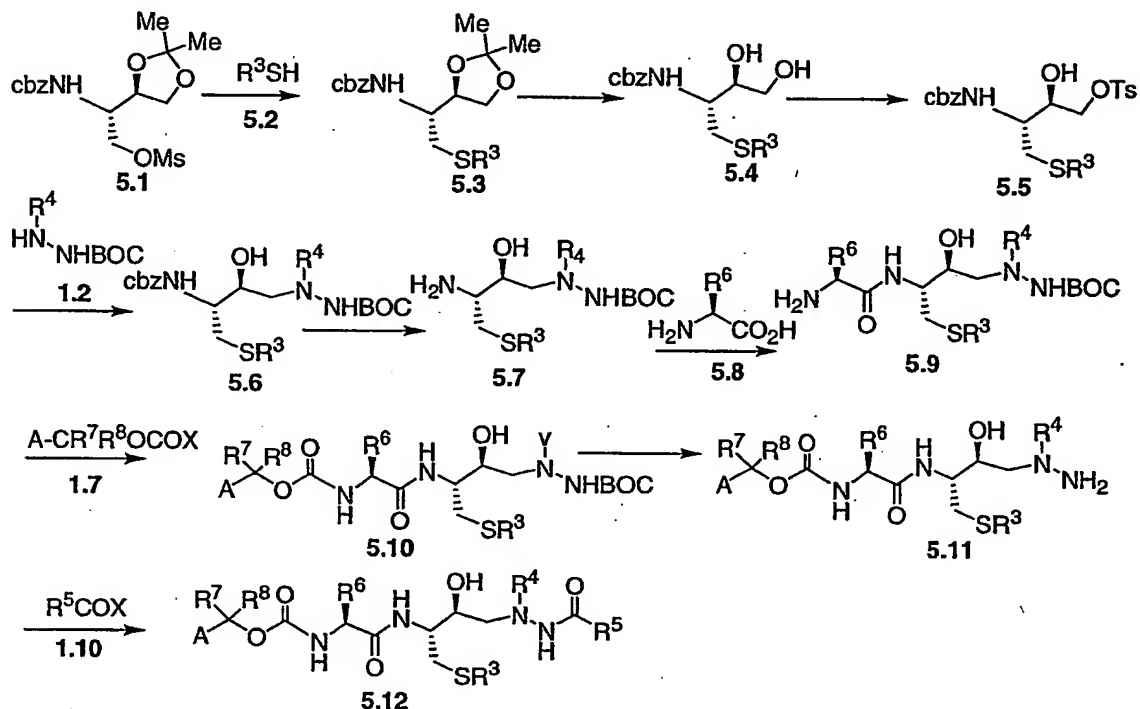
The latter compound is then reacted with the hydrazine derivative 1.2 to afford the hydrazine 5.6. The displacement reaction is conducted in a polar aprotic solvent such as

dimethylformamide, acetonitrile, dioxan and the like, in the presence of an organic or inorganic base, to afford the product 5.6. Preferably, equimolar amounts of the reactants are combined in dimethylformamide at ca. 80° in the presence of potassium carbonate, to produce the hydrazine product 5.6. The cbz protecting group is then removed to afford the amine 5.7. The
5 removal of carbobenzyloxy substituents to afford the corresponding amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 335. The conversion can be effected by the use of catalytic hydrogenation, in the presence of hydrogen or a hydrogen donor and a palladium catalyst. Alternatively, the cbz group can be removed by treatment of the substrate with triethylsilane, triethylamine and a
10 catalytic amount of palladium (II) chloride, as described in Chem. Ber., 94, 821, 1961, or by the use of trimethylsilyl iodide in acetonitrile at ambient temperature, as described in J. Chem. Soc., Perkin Trans. I, 1277, 1988. The cbz group can also be removed by treatment with Lewis acid such as boron tribromide, as described in J. Org. Chem., 39, 1247, 1974, or aluminum chloride, as described in Tet. Lett., 2793, 1979. Preferably, the cbz protecting
15 group is removed by hydrogenation of the substrate 5.6 in the presence of 5% palladium on carbon catalyst, to yield the amine 5.7. The amine is then coupled with the aminoacid 5.8 to give the amine 5.9. The reaction is effected under the same conditions as described above for the preparation of the amide 1.6.

The amine is then reacted with a reagent A-CR⁷R⁸OCOX (1.7), in which the substituent A is
20 the group (R¹O)₂P(O)-link, or a precursor group thereto, such as [OH], [SH], [NH], Br, as described below, and in which the substituent X is a leaving group, to yield the carbamate 5.10. The reagent A-CR⁷R⁸OCOX is derived from the corresponding alcohol A-CR⁷R⁸OH, using methods described below, (Scheme 20). The preparation of the reactants A-CR⁷R⁸OCOX is described in Schemes 21 - 26. The preparation of carbamates by means of
25 reactions between alcohols and amines is described below, in Scheme 20.

The BOC protecting group is then removed from the product 5.10 to produce the hydrazine 5.11. The conditions for the removal of the BOC group are the same as those described above (Scheme 1). The product is then acylated with the carboxylic acid or activated derivative thereof, 1.10, using the conditions described above, (Scheme 1) to yield the product 5.12.
30 The procedures illustrated in Scheme 5 depict the preparation of the compounds 5.11 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 6 illustrates the conversion of compounds 5.12 in which

Scheme 5


$$\text{5.12} \xrightarrow{(R^1O)_2P(O)\text{-link}} \text{1}$$

Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

- 10 Schemes 7 and 8 illustrate the preparation of the phosphonate esters 2 in which X is a direct bond. As shown in Scheme 7, a cbz-protected oxirane 7.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, is reacted with a hydrazine derivative 1.2, to afford the ring-opened product 7.3. The conditions for the reaction are the same as those described above for the preparation of the hydrazine derivative

1.3, (Scheme 1). The preparation of the substituted oxiranes 7.1 are described below, in Scheme 9. The product 7.3 is then transformed, using the sequence of reactions illustrated in Scheme 7, into the product 7.8. The conditions employed for the component reactions of this sequence are the same as for the analogous reaction in Scheme 1.

5

The procedures illustrated in Scheme 7 depict the preparation of the compounds 7.8 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 8 illustrates the conversion of compounds 7.8 in which A is a precursor to the group $\text{link-P(O)(OR}^1)_2$ into the compounds 2. Procedures for the conversion of the substituent A into the group $\text{link-P(O)(OR}^1)_2$ are illustrated below, (Schemes 21 - 56).

10

Scheme 9 illustrates the preparation of the oxiranes 7.1. In this sequence, a substituted phenylalanine 9.1, in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below, is transformed into the cbz-protected derivative 9.2, using the conditions described above for the preparation of the cbz derivative 3.2, (Scheme 3). The latter compound is then transformed, using the sequence of reactions illustrated in Scheme 3, into the product 7.1. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 3.

15

20

Preparation of the phosphonate ester intermediates 2 in which X is a sulfur.

Schemes 10 and 11 illustrate the preparation of the compounds 2 in which X is sulfur. As shown in Scheme 10, the mesylate 5.1 is reacted with the substituted thiophenol 10.1, in which substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below (scheme 30-39), to afford the thioether 10.2. The conditions employed for this reaction are the same as those described above for the preparation of the thioether 5.3, Scheme 5. The product 10.2 is then transformed, using the series of reactions shown in Scheme 5, into the diacylated thioether 10.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5.

25

30

The procedures illustrated in Scheme 10 depict the preparation of the compounds 10.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as

[OH], [SH] Br, as described below. Scheme 11 illustrates the conversion of compounds 10.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes 12 and 13 depict the preparation of the phosphonate esters 3a in which X is a direct bond. As shown in Scheme 12, the oxirane 1.1 is reacted with a BOC protected phenylhydrazine derivative 12.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. The preparation of the hydrazine derivatives 12.1 is described in Schemes 4, 40 and 41. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine 7.3, Scheme 7. The product 12.2 is then transformed, using the sequence of reactions shown in Scheme 7 for the transformation of the hydrazine 7.3 into the diacylated compound 7.8, into the diacylated compound 12.3. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 7.

The procedures illustrated in Scheme 12 depict the preparation of the phosphonate esters 12.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 13 illustrates the conversion of compounds 12.3 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 3a in which X is a direct bond. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

The phosphonate esters 3b, 3c and 3d, in which X is a direct bond, are prepared using the procedures of Schemes 12 and 13, except that the hydrazine derivatives 4.13, 4.17 and 4.15, prepared as described in Schemes 42 - 52, are used in place of the hydrazine derivative 12.1.

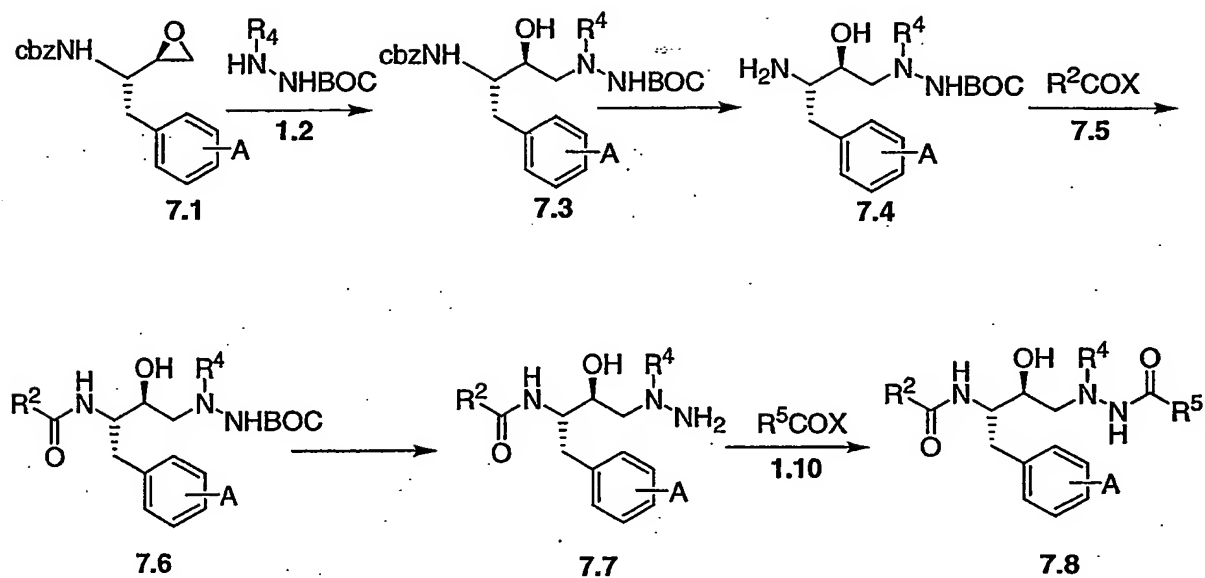
Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

Schemes 14 and 15 illustrate the preparation of the phosphonate esters 3a in which X is sulfur.

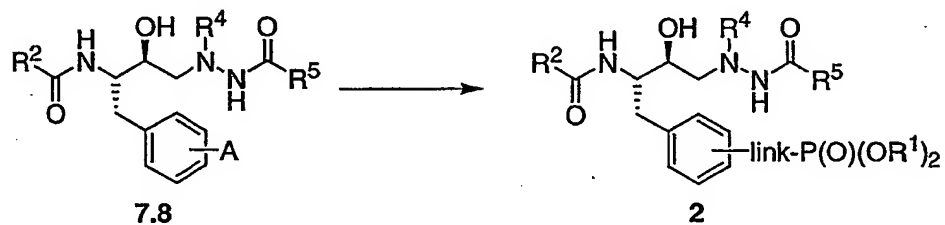
- 5 As shown in Scheme 14, the p-toluenesulfonate ester 5.5 is reacted with the phenylhydrazine derivative 12.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below, to afford the hydrazine derivative 14.1. The reaction is conducted under the same conditions as described above for the preparation of the hydrazine 5.6, Scheme 5. The product 14.1 is then transformed into the diacylated
- 10 product 14.2, using the sequence of reactions shown in Scheme 5. The conditions for the component reactions of this sequence are the same as for the analogous reactions in Scheme 5. The procedures illustrated in Scheme 14 depict the preparation of the phosphonate esters 14.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 15 illustrates the conversion of compounds 14.2
- 15 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 3a in which X is S. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 21 - 56).

- The phosphonate esters 3b, 3c and 3d, in which X is S, are prepared using the procedures of Schemes 12 and 13, except that the hydrazine derivatives 4.13, 4.17 and 4.15, prepared as
- 20 described in Schemes 42 - 52, are used in place of the hydrazine derivative 12.1.

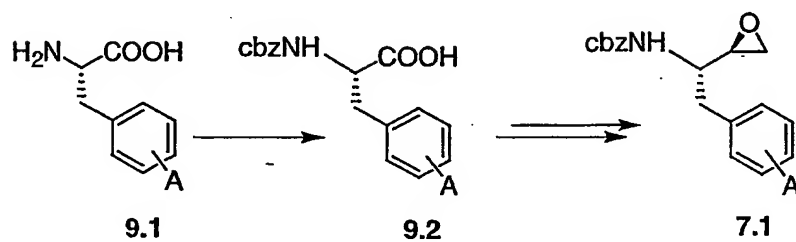
Scheme 7



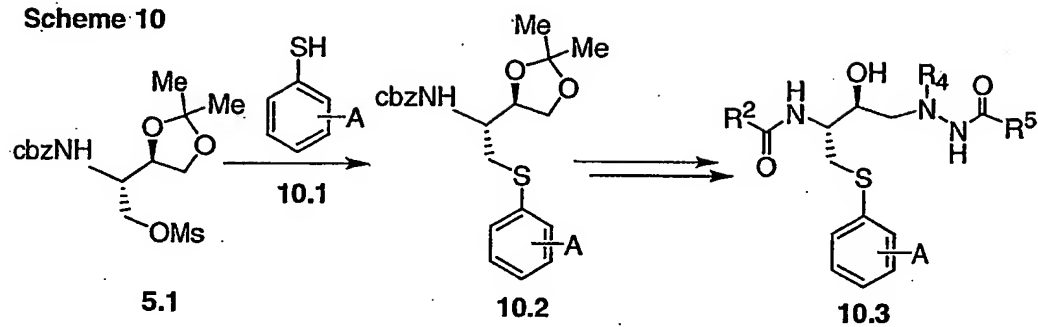
Scheme 8



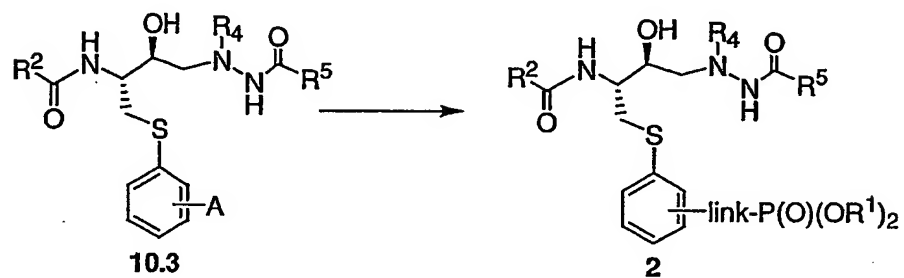
Scheme 9



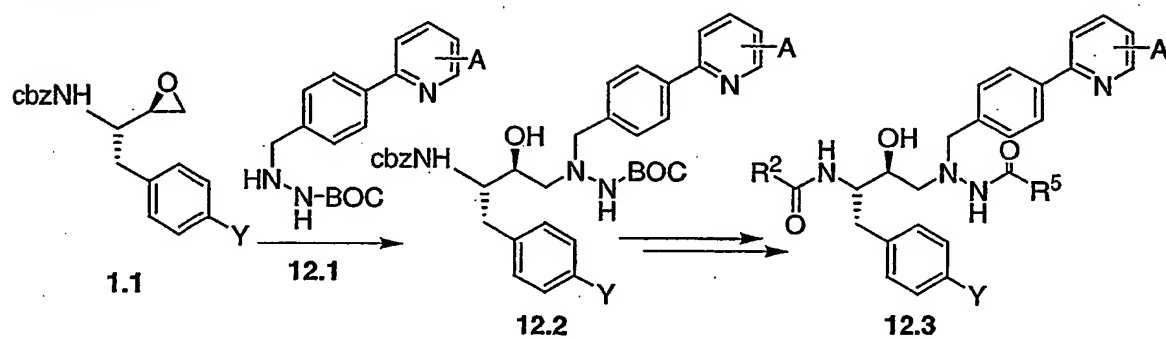
Scheme 10



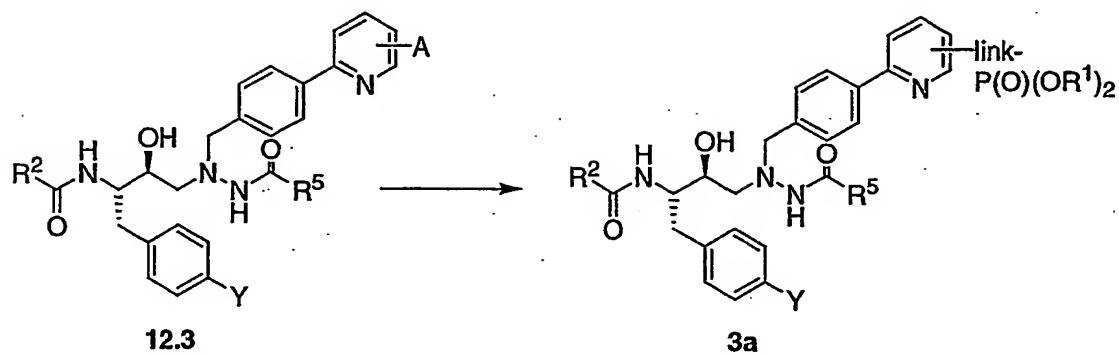
Scheme 11



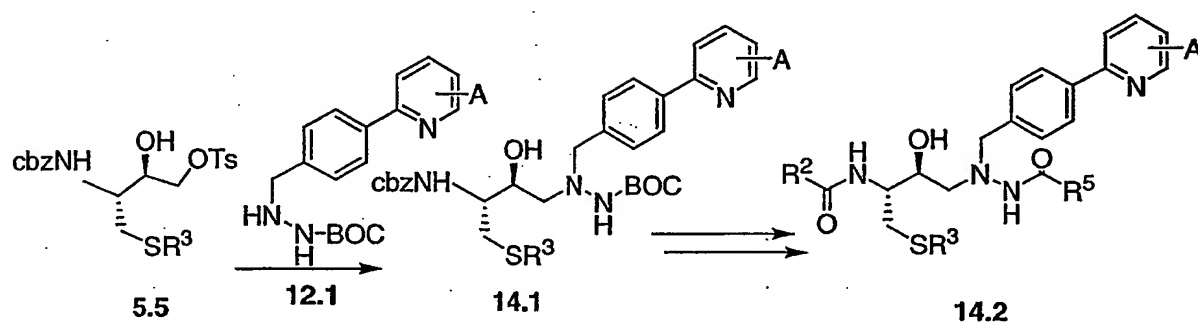
Scheme 12



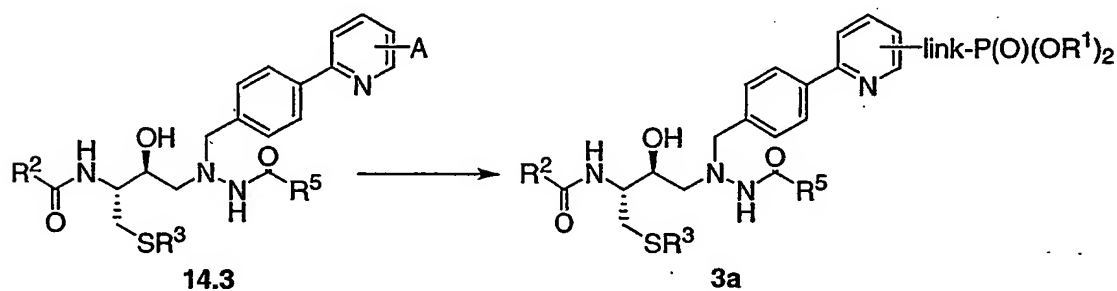
Scheme 13



Scheme 14



Scheme 15



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

5

Schemes 16 and 17 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond. As shown in Scheme 16, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid or activated derivative thereof R^2COX 7.5, to afford the amide 16.1. The conditions for the amide forming reaction are the same as those described above for the

preparation of the amide 1.11, (Scheme 1). The product is then deprotected by removal of the BOC group, using the procedures described above (Scheme 1), to yield the hydrazine 16.2.

This material is then coupled with the aminoacid 1.5, using the coupling procedures described above for the preparation of the amide 1.6, to produce the amide 16.3. The product is then
5 reacted with the acylating agent $A-CR^7R^8OCOX$, 1.7, in which A and X are as described above, Scheme 1, to afford the carbamate product 16.4.

The procedures illustrated in Scheme 16 depict the preparation of the phosphonate esters 16.4 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 17 illustrates the conversion of compounds 16.4
10 in which A is a precursor to the group $link-P(O)(OR^1)_2$ into the compounds 4. Procedures for the conversion of the substituent A into the group $link-P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

15 Schemes 18 and 19 illustrate the preparation of the phosphonate esters 4 in which X is sulfur. As shown in Scheme 18, the amine 5.7, prepared as described in Scheme 5, is reacted with the carboxylic acid or activated derivative thereof 7.5, to produce the amide 18.1. The reaction is performed under the conditions described above for the preparation of the amide 1.11. The
20 BOC group present in the amide 18.1 is then removed using the procedures described above, (Scheme 1) to afford the amine 18.2. This material is then coupled with the aminoacid 1.5, using the procedures described above for the preparation of the amide 1.6, to produce the amide 18.3. The latter compound is then reacted with the acylating agent $A-CR^7R^8OCOX$, 1.7, in which A and X are as described above, Scheme 1, to afford the carbamate product
25 18.4.

The procedures illustrated in Scheme 18 depict the preparation of the phosphonate esters 18.4 in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19 illustrates the conversion of compounds 18.4
30 in which A is a precursor to the group $link-P(O)(OR^1)_2$ into the compounds 4. Procedures for the conversion of the substituent A into the group $link-P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56).

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

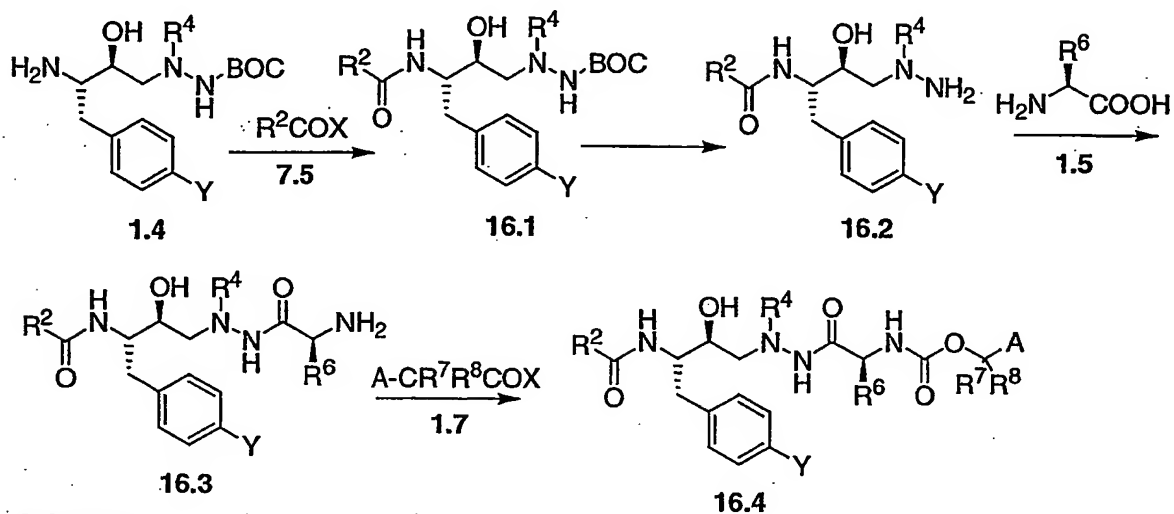
Schemes 19a and 19b illustrate the preparation of the phosphonate esters 5 in which X is a direct bond. As shown in Scheme 19a, the amine 1.6 is reacted with a quinoline-2-carboxylic acid derivative 19a.1, in which the substituent A is either the group $(R^1O)_2P(O)$ -link or a precursor group thereto, such as OH, SH, Br to afford the amide 19a.2. The reaction is performed as described above for the preparation of the amide 1.6 (Scheme 1). The BOC protecting group is then removed, using the procedures described in Scheme 1, to yield the amine 19a.3. This compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19a.5. The procedures illustrated in Scheme 19a depict the preparation of the phosphonate esters 19a.5 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19b illustrates the conversion of compounds 19a.5 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents 19a.1 is described below, (Schemes 53 - 56).

Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

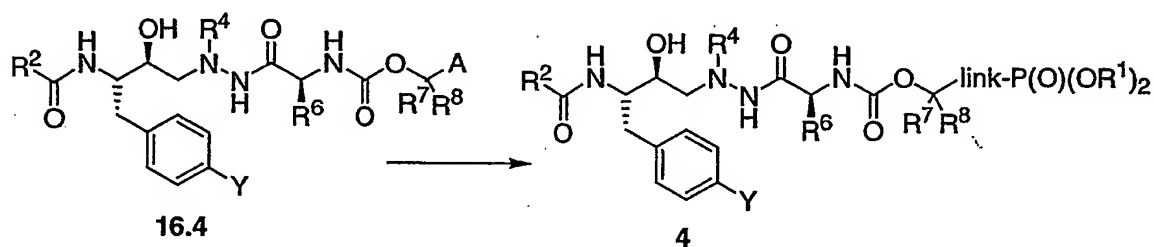
Schemes 19c and 19d illustrate the preparation of the phosphonate esters 5 in which X is sulfur. As shown in Scheme 19c, the amine 5.9 is reacted, as described above, with the quinoline carboxylic acid derivative 19a.1 to yield the amide product 19c.1. The BOC protecting group is then removed, as described above, to give the amine 19c.2. The latter compound is then reacted, as described above, with the carboxylic acid R^5COOH , or an activated derivative thereof 19a.4, to give the amide 19c.3. The procedures illustrated in Scheme 19c depict the preparation of the phosphonate esters 19c.3 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH] Br, as described below. Scheme 19d illustrates the conversion of compounds 19c.3 in which A is a precursor to the group link- $P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituent A into the group link- $P(O)(OR^1)_2$ are

illustrated below, (Schemes 21 - 56). The preparation of the quinoline carboxylic acid reagents **19a.1** is described below, (Schemes 53 - 56).

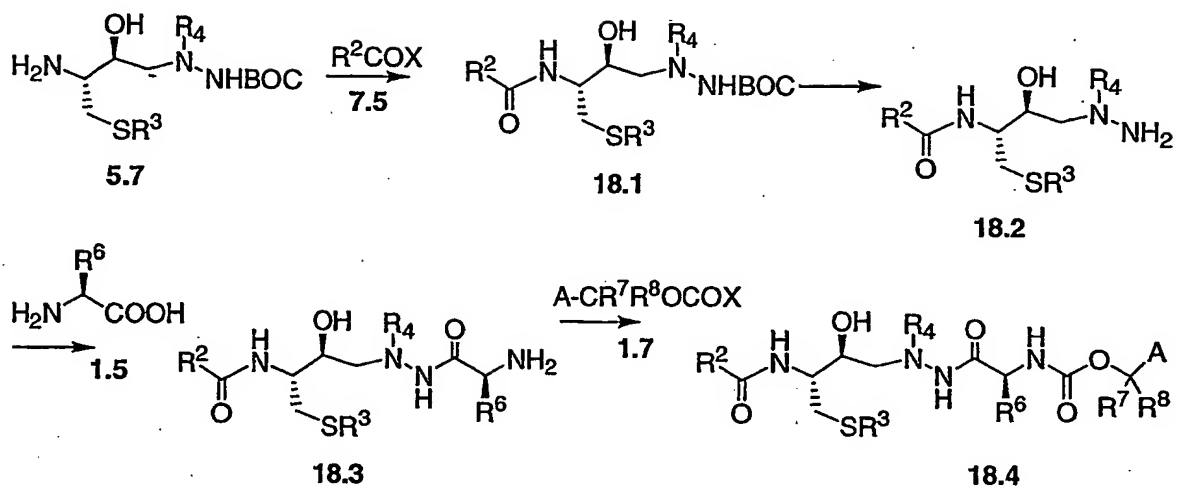
Scheme 16



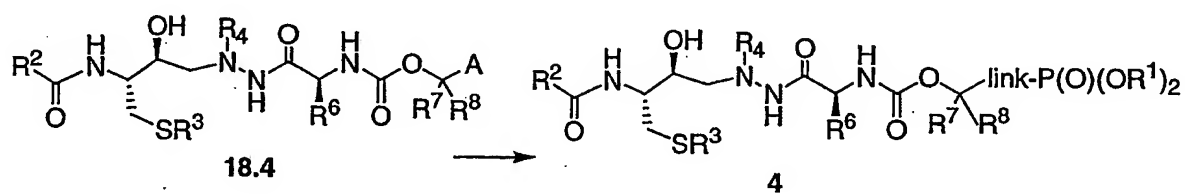
Scheme 17



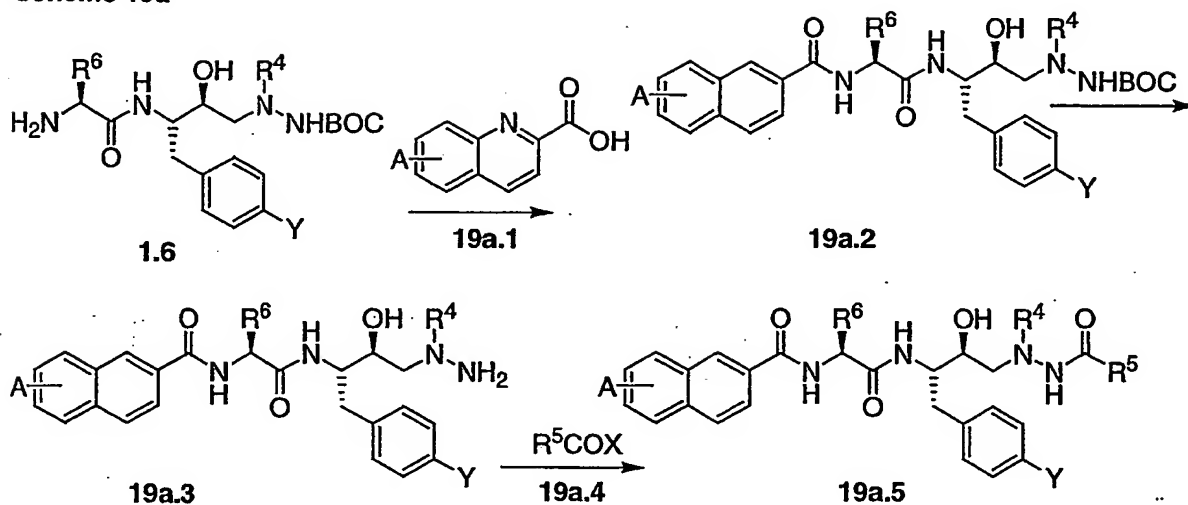
Scheme 18



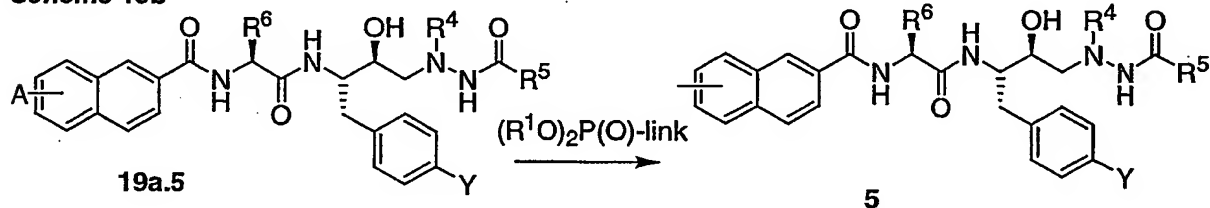
Scheme 19



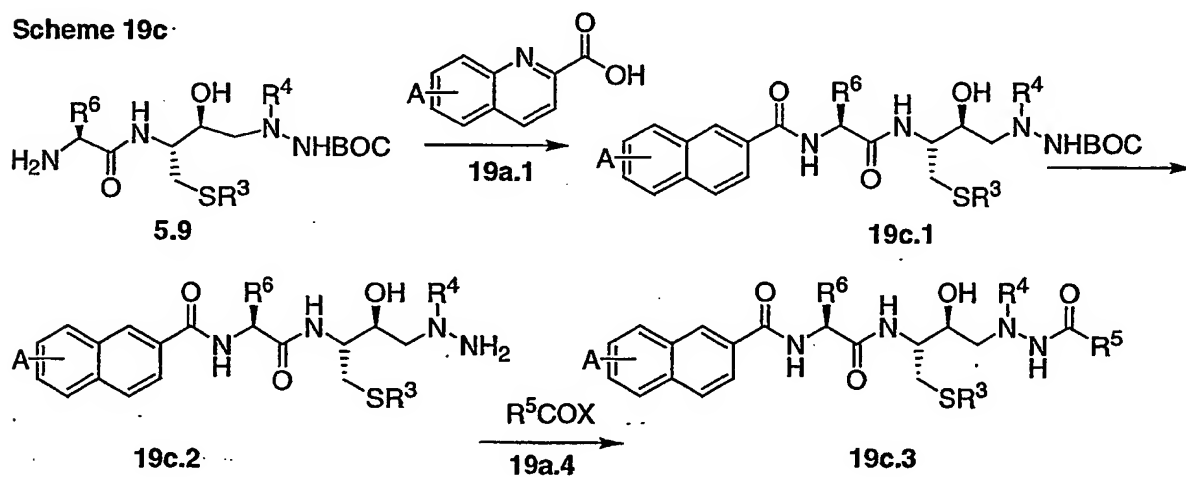
Scheme 19a



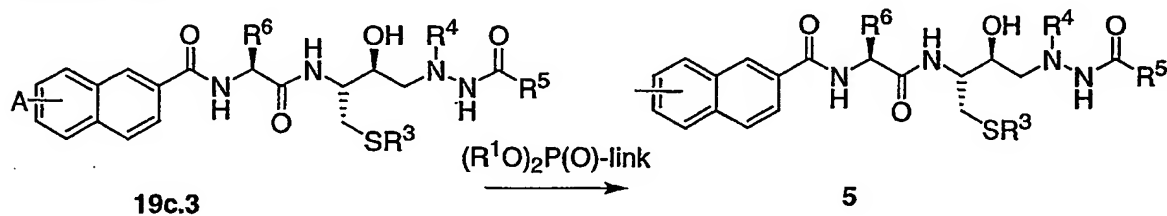
Scheme 19b



Scheme 19c



Scheme 19d



Preparation of carbamates.

The phosphonate esters **1** and **4**, and the phosphonate ester **1-7** in which the R^2CO or R^5CO groups are formally derived from the carboxylic acids **C38 - C49** (Chart 2c) contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 20 illustrates various methods by which the carbamate linkage can be synthesized. As shown in Scheme 20, in the general reaction generating carbamates, a carbinol **20.1**, is converted into the activated derivative **20.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative **20.2** is then reacted with an amine **20.3**, to afford the carbamate product **20.4**. Examples 1 - 7 in Scheme 20 depict methods by which the general reaction can be effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 20, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol **20.5**. In this procedure, the carbinol **20.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **20.6**. The latter compound is then reacted with the amine component **20.3**, in the presence of an organic or inorganic base, to afford the carbamate **20.7**. For example, the chloroformyl compound **20.6** is reacted with the amine **20.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **20.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 20, Example 2 depicts the reaction of the chloroformate compound **20.6** with imidazole to produce the imidazolide **20.8**. The imidazolide product is then reacted with the amine **20.3** to yield the carbamate **20.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is

conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 20 Example 3, depicts the reaction of the chloroformate 20.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 20.10. The reaction is

5 conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 20.19 - 20.24 shown in Scheme 20, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 20.19, N-hydroxysuccinimide 20.20, or pentachlorophenol, 20.21, the mixed carbonate 20.10 is obtained by the reaction of the
10 chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 20.22 or 2-hydroxypyridine 20.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

15 Scheme 20 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 20.8 is employed. In this procedure, a carbinol 20.5 is reacted with an equimolar amount of carbonyl diimidazole 20.11 to prepare the intermediate 20.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 20.8 is then reacted with an equimolar amount of the
20 amine R'NH₂ to afford the carbamate 20.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 20.7.

Scheme 20, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benztriazole 20.13. In this procedure, a carbinol ROH is reacted at ambient
25 temperature with an equimolar amount of benztriazole carbonyl chloride 20.12, to afford the alkoxy carbonyl product 20.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine R'NH₂ to afford the carbamate 20.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
30 to about 80° as described in Syn., 1977, 704.

Scheme 20, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 20.14, is reacted with a carbinol 20.5 to afford the intermediate alkyloxycarbonyl

intermediate **20.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **20.7**. The procedure in which the reagent **20.15** is derived from hydroxybenztriazole **20.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **20.15** is derived from N-hydroxysuccinimide **20.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **20.15** is derived from 2-hydroxypyridine **20.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **20.15** is derived from 4-nitrophenol **20.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **20.14** is conducted in an inert organic solvent at ambient temperature.

10 Scheme **20**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **20.16**. In this procedure, an alkyl chloroformate **20.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **20.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **20.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for
15 example as described in Syn., 1982, 404.

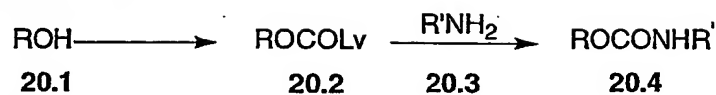
Scheme **20**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **20.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent
20 such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **20.7**.

Scheme **20**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **20.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants
25 are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **20.7**.

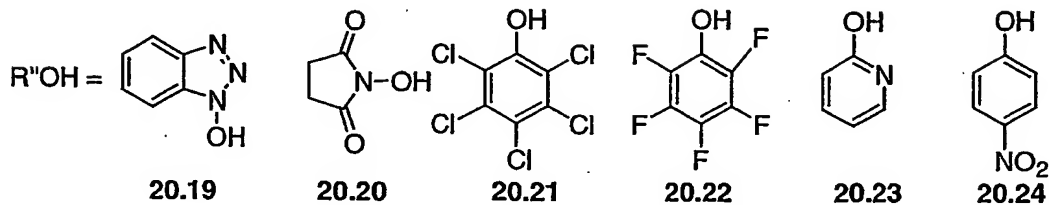
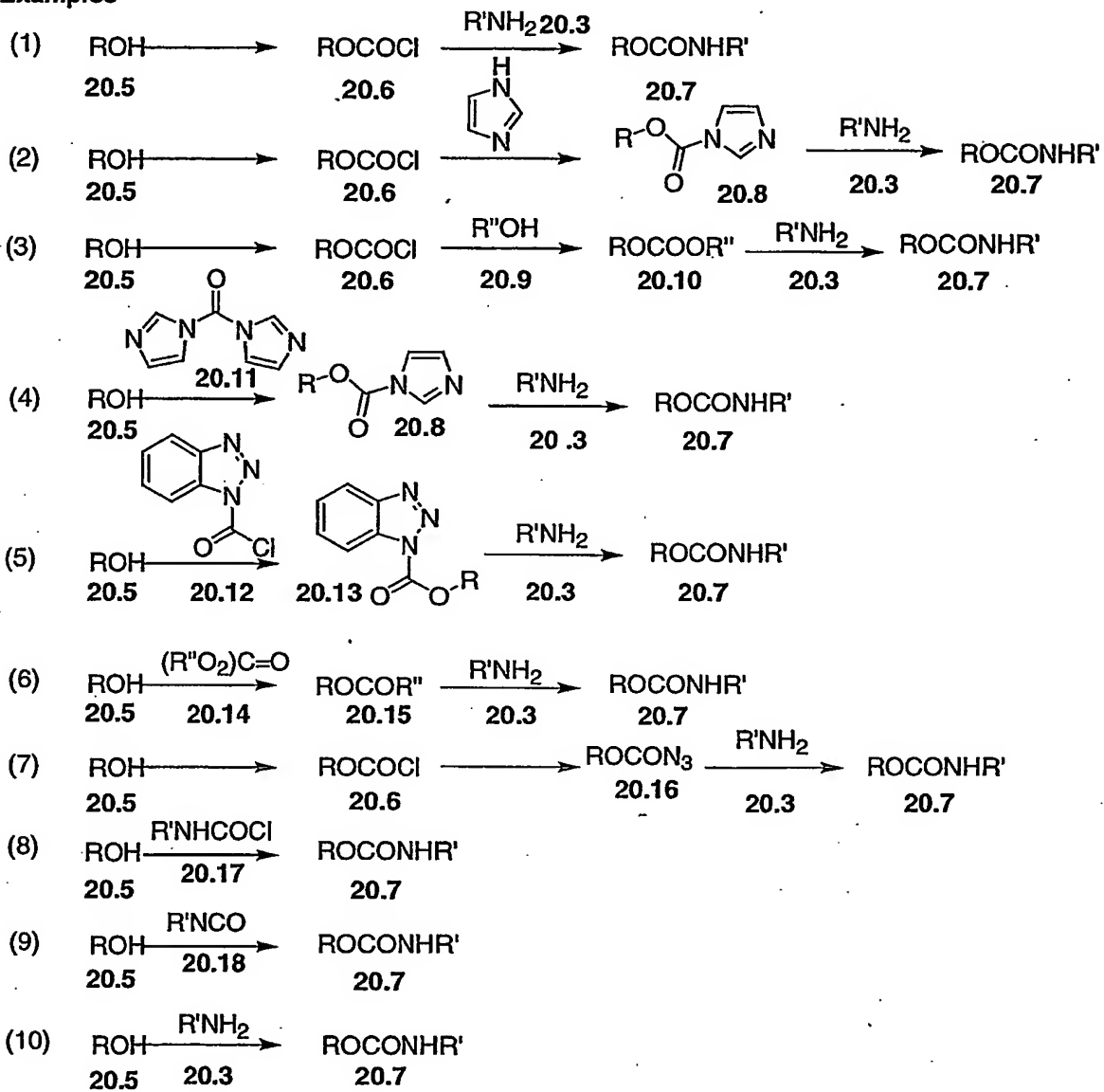
Scheme **20**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic
30 solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **20.7**.

Scheme 20

General reaction



Examples



Preparation of the reagents A-CR⁷R⁸OCOX.

The reagents A-CR⁷R⁸OCOX **1.7** are prepared from the corresponding carbinols A-CR⁷R⁸OH, using procedures such as those described above in Scheme 20. Examples of the preparation of the carbinols A-CR⁷R⁸OH and the derived reagents **1.7** are shown below in Schemes 21-26. The activation methods for the conversion of the carbinols A-CR⁷R⁸OH to the reagents A-CR⁷R⁸OCOX are interchangeable between the different alcohols A-CR⁷R⁸OH.

Scheme 21 depicts the preparation of phosphonate-containing reagents **21.2** in which the phosphonate is linked by means of an alkylene chain. In this procedure, a dialkyl hydroxyalkyl phosphonate **21.1** is reacted with phosgene, or an equivalent reagent, to afford the chloroformate **21.2**, as described above in Scheme 20, Example 1. The reaction is conducted in an inert organic solvent such as dichloromethane or toluene, at from about 0° to ambient temperature.

For example, as shown in Scheme 21, Example 1, a dialkyl hydroxymethylphosphonate **21.3** (Aldrich) is reacted with excess phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 197, 1965, to afford the chloroformyl product **21.4**.

Scheme 21, Example 2 illustrates the analogous conversion of a dialkyl hydroxyethyl phosphonate **21.5** (Aldrich) into the chloroformate derivative **21.6**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Scheme 21, Example 3 illustrates the analogous conversion of a dialkyl phosphono-substituted tert. butanol **21.7**, prepared as described in Fr.2462440, into the chloroformate derivative **21.8**. The reaction is performed as described above for the preparation of the chloroformate **21.4**.

Using the above procedures, but employing, in place of the phosphonates **21.3**, **21.5** or **21.7**, different dialkyl hydroxyalkyl phosphonates **21.1**, the corresponding products **21.2** are obtained.

Scheme 22 depicts the preparation of phosphonate-containing reagents **22.2** in which the phosphonate is linked by means of a phenyl ring. In this procedure, a dialkyl

hydroxyalkylphenyl phosphonate 22.1 is converted, as described above, into an activated chloroformyl derivative 22.2, using the procedures described above in Scheme 20.

For example, a dialkyl 4-hydroxymethylphenylphosphonate 22.3 (Aldrich) is reacted in tetrahydrofuran with an equimolar amount of the 2-pyridyl carbonate 22.4, prepared as
5 described in Tet. Let., 1991, 4251, to afford the product 22.5.

Using the above procedure, but employing, in place of a dialkyl hydroxyphenylphosphonate 22.3, different dialkyl hydroxyphenyl phosphonates 22.1, the corresponding products 22.2 are obtained.

10 Scheme 23 depicts the preparation of phosphonate containing reagents 23.4 in which the phosphonate group is linked by means of an alkylene chain incorporating a heteroatom O, S or N. In this procedure, a dialkyl hydroxy-, thio- or alkylaminoalkylphosphonate 23.1 is alkylated by reaction with a bromoalkanol 23.2. The alkylation reaction is conducted at from ambient temperature to about 70° in a polar organic solvent such as dimethylformamide,
15 dioxan or acetonitrile, in the presence of a base. In cases in which X is oxygen, a strong base such as lithium hexamethyldisilylazide or potassium tert-butoxide is employed. In cases in which X is sulfur or alkylamino, an inorganic base such as potassium carbonate or cesium carbonate is used. The product 23.3 is then converted into an activated derivative 23.4 by means of one of the methods described above in Scheme 20.

20 For example, as shown in Scheme 23, Example 1, a dialkyl 2-mercaptoethylphosphonate 23.5, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, is reacted with one molar equivalent of bromoethanol 23.6, in dimethylformamide at 60° in the presence of cesium carbonate, to afford the thioether product 23.7. This compound is then reacted with pentafluorophenyl carbonate 23.8, (Fluorochem) in dimethylformamide solution at ambient
25 temperature in the presence of triethylamine, to afford the pentafluorophenoxycarbonyl product 23.9.

As a further example of the method of Scheme 23, as shown in Example 2, a dialkyl methylaminomethyl phosphonate 23.10, (AsInEx Inc.) is reacted in dimethylformamide at 70° with one molar equivalent of 5-bromo-2-hydroxy-2-methylpentane 23.11, prepared as
30 described in J. Med. Chem., 1994, 37, 2343, and potassium carbonate, to afford the amine product 23.12. The product is then converted, as described above, into the pentafluorophenyl formate derivative 23.13.

Using the above procedures, but employing, in place of a dialkyl 2-mercaptoethylphosphonate 23.5, or a dialkyl methylaminomethyl phosphonate 23.10, different hydroxy, mercapto or aminoalkylphosphonates 23.1, and/or different bromoalkanols 23.2, and/or different activation methods, the corresponding products 23.4 are obtained.

5

Scheme 24 illustrates the preparation of phosphonate containing reagents 24.4 in which the phosphonate group is linked by means of an alkylene chain incorporating an N-alkyl group. In this procedure, a dialkyl formylalkyl phosphonate 24.1 is reacted with an alkylaminoalkanol 24.2 under reductive amination conditions, so as to afford the product 24.3. The preparation of amines by means of reductive amination procedures is described, for example, in
10 Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 269. In this reaction, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride,
15 sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The reduction reaction can also be performed by hydrogenation in the presence of a palladium catalyst and hydrogen or a hydrogen donor. The reaction product 24.3 is then transformed into the activated derivative 24.4 by means of one of the procedures described above in
20 Scheme 20.

As shown in Scheme 24, Example 1, a dialkyl formylmethylphosphonate 24.5 (Aurora) is reacted with methylaminoethanol 24.6, in the presence of sodium cyanoborohydride, to afford the coupled product 24.7. This compound is then reacted with an equimolar amount of chlorocarbonylbenztriazole 20.13, in toluene at 80°, in the presence of one molar equivalent of
25 triethylamine, as described in Syn., 1977, 704, to yield the product 24.8.

As a further example of the method of Scheme 24, as shown in Example 2, the aldehyde 24.5 is reacted with 2-hydroxy-2-methyl-3-methylaminopropane 24.10, under reductive amination conditions, to afford the amine product 24.11. The latter compound is then reacted with phosgene, or an equivalent thereof, as described above, to afford the chloroformyl product
30 24.12.

Using the above procedures, but employing, in place of the phosphonates 24.5, different phosphonates 24.1, and/or in place of the aminoalkanols 24.6 or 24.10, different

aminoalkylalkanols 24.2, and/or different activation methods described in Scheme 20, the corresponding products 24.4 are obtained.

Scheme 25 illustrates the preparation of phosphonate containing reagents 25.2 in which the phosphonate group is linked by means of an alkylene chain incorporating an acetylenic linkage. In this procedure, a dialkyl hydroxyalkynyl phosphonate 25.1 is converted, by means of one of the procedures described in Scheme 20, into the activated formyl derivative 25.2.

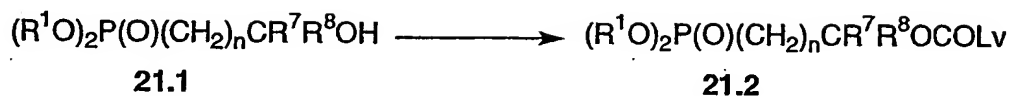
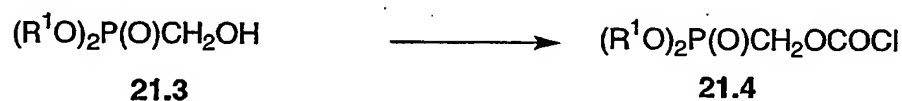
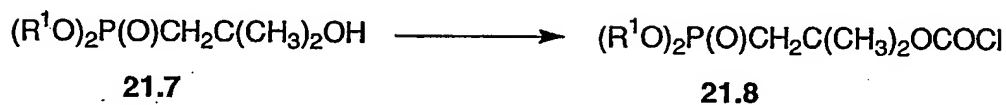
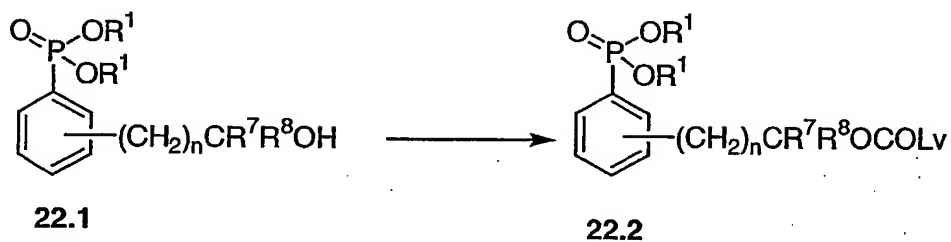
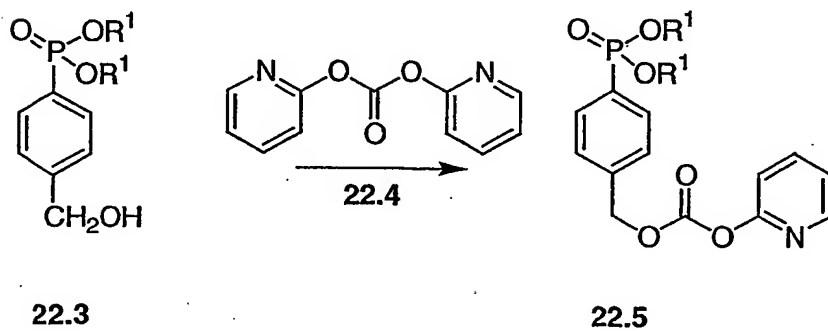
For example, a dialkyl hydroxypropynyl phosphonate 25.3 prepared as described in J. Org. Chem., 1987, 52, 4810, is reacted with one molar equivalent of di(succinimidyloxy)carbonate 25.4, prepared as described in Tet. Lett, 1992, 2781, in dichloromethane at ambient temperature, to afford the product 25.5.

Using the above procedures, but employing, in place of the dialkyl hydroxypropynyl phosphonate 25.3, different dialkyl hydroxyalkynyl phosphonates 25.1, the corresponding products 25.2 are obtained.

Scheme 26 illustrates the preparation of phosphonate containing reagents 26.2 in which the phosphonate group is linked by means of an alkylene chain incorporating an olefinic linkage. In this procedure, a dialkyl hydroxyalkenyl phosphonate 26.1 is converted, by means of one of the procedures described in Scheme 20, into the activated formyl derivative 26.2.

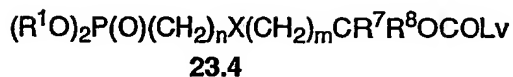
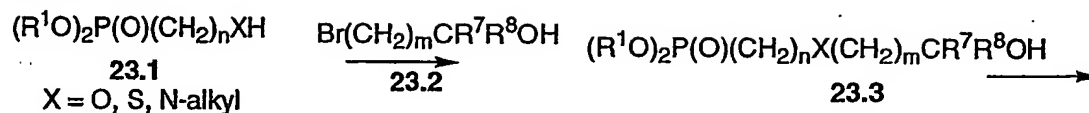
For example, a dialkyl propenylphosphonate 26.3, prepared as described in Zh. Obschei. Khim., 1974, 44, 18343, is reacted with phosgene in toluene at 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to afford the chloroformyl product 26.4.

Using the above procedures, but employing, in place of the dialkyl hydroxypropenyl phosphonate 26.3, different dialkyl hydroxyalkenyl phosphonates 26.1, the corresponding products 26.2 are obtained.

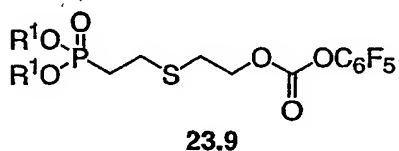
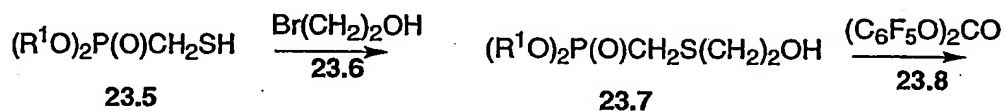
Scheme 21**Method****Example 1****Example 2****Example 3****Scheme 22****Method****Example**

Scheme 23

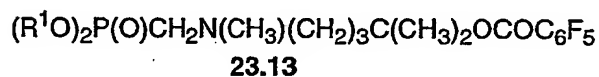
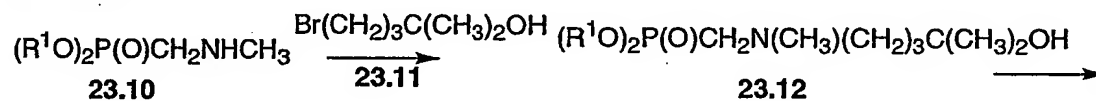
Method



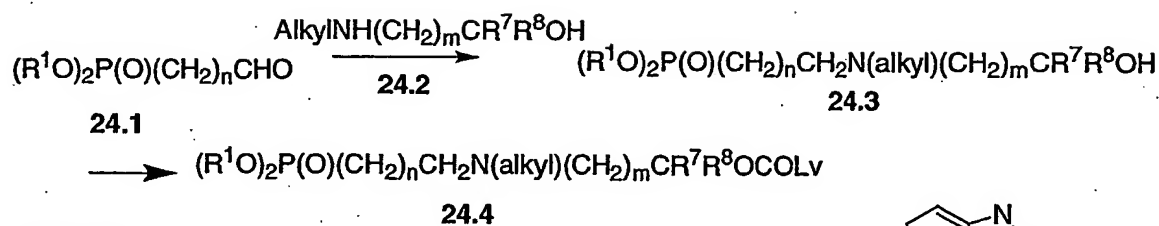
Example 1



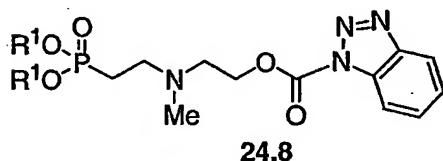
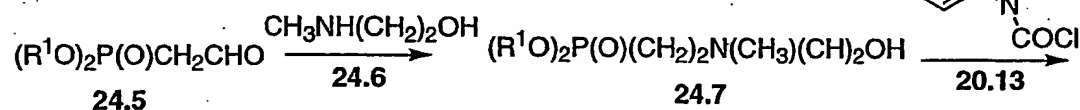
Example 2



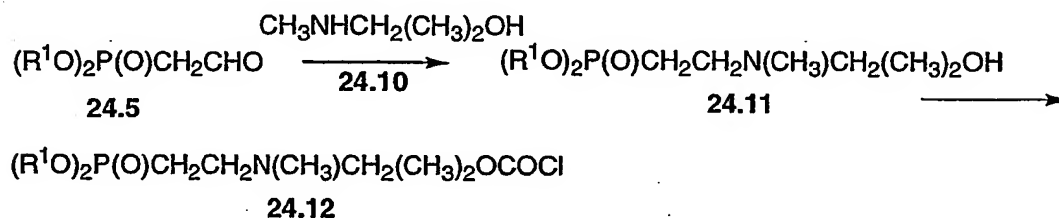
Scheme 24
Method



Example 1

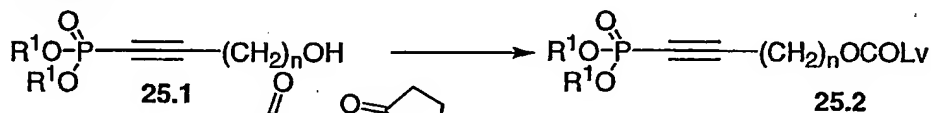


Example 2

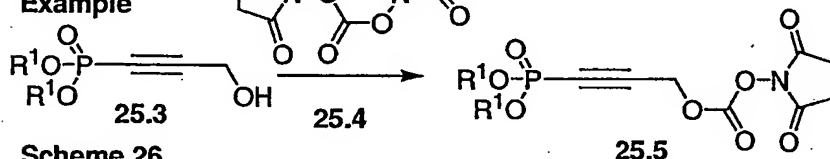


Scheme 25

Method

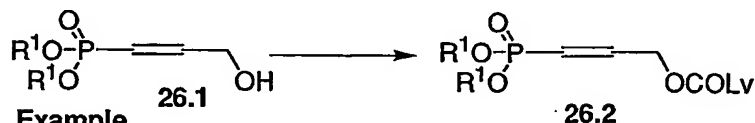


Example

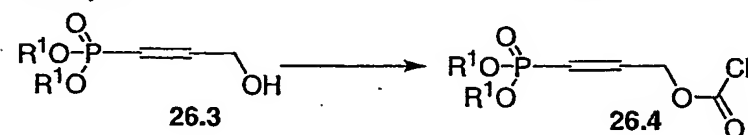


Scheme 26

Method



Example



Preparation of the oxirane reactants 7.1.

5 The oxirane reactants 7.1 are obtained by means of chemical transformations applied to variously substituted phenylalanine derivatives. In the methods described below, the phosphonate moiety can be introduced into the molecule at any appropriate stage in the synthetic sequence, or after the intermediates are incorporated into the phosphonate esters 2.

10 Scheme 27 depicts the preparation of oxirane reactants 27.5 in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 27.1 is converted into the cbz-protected derivative, using the procedures described above in Scheme 3. The protected product 27.2 is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane 27.3. The latter compound is then reacted with a dialkyl
15 phosphite 27.4, in the presence of a palladium catalyst, to afford the phosphonate ester 27.5. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

For example, 4-bromophenylalanine 27.6, prepared as described in Biotech. Lett., 1994, 16, 373, is converted, as described above, (Scheme 3), into the oxirane 27.7. This compound is
20 then reacted, in toluene solution at reflux, with a dialkyl phosphite 27.4, triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 27.8.

Using the above procedures, but employing, in place of 4-bromophenylalanine 27.6, different bromo-substituted phenylalanines 27.1, and/or different dialkyl phosphites, the corresponding
25 products 27.5 are obtained.

Scheme 28 illustrates the preparation of oxiranes 28.4 in which the phosphonate moiety is attached by means of an alkylene chain. In this procedure, a carbobenzyloxy protected bromo-substituted phenylalanine 27.2, prepared as described above, is coupled, in the presence of a
30 palladium catalyst, with a dialkyl alkenylphosphonate 28.1, to afford the coupled product 28.2. The preparation of aryl alkenyl phosphonates by means of a coupling reaction between aryl bromides and alkenyl phosphonates is described in Syn., 1983, 556. The reaction is performed

in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a palladium (II) catalyst, a tertiary base such as triethylamine and a phosphine such as triphenylphosphine and the like, to afford the aryl alkenyl phosphonate product 28.2. The latter compound is then reduced, for example by reaction with diimide, as described in
5 Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 262, to afford the saturated product 28.3. The latter compound is then converted, by means of the series of reactions shown in Scheme 3, into the oxirane 28.4.

For example, the cbz-protected 3-bromophenylalanine 28.5, prepared as described in Pept. Res., 1990, 3, 176, is coupled, in acetonitrile solution at 100° in a sealed tube, with a dialkyl
10 vinylphosphonate 28.6, in the presence of palladium (II)acetate, tri-(o-tolyl)phosphine and triethylamine, as described in Syn., 1983, 556, to afford the coupled product 28.7. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product 28.8. This material is then converted, using the procedures shown in Scheme 3, into
15 the oxirane 28.9.

Using the above procedures, but employing, in place of the 3-bromophenylalanine derivative 28.5, different bromo compounds 27.2, and/or different alkenyl phosphonates 28.1, the corresponding products 28.4 are obtained.

20 Scheme 29 illustrates the preparation of oxiranes 29.9 in which the phosphonate group is linked by means of an alkylene chain and an oxygen or sulfur atom. In this procedure, a substituted phenylalanine 29.1 is converted into the methyl ester 29.2 by means of a conventional acid-catalyzed esterification reaction. The hydroxy or mercapto substituent is then protected to afford the derivative 29.3. The protection of phenyl hydroxyl and mercapto
25 groups is described respectively, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by
30 T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl, 9-fluorenylmethyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-

methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected compound 29.3 is then transformed into the cbz derivative 29.4, using the procedure described above (Scheme 3). The O or S-protecting group is then removed to produce the phenol or thiol 29.5. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978 or by the use of mercuric acetate in trifluoroacetic acid. The resultant phenol or thiophenol 29.5 is then reacted with a dialkyl halo or alkylsulfonyloxyalkyl phosphonate 29.6, to yield the ether or thioether product 29.7. The alkylation reaction is performed at from ambient temperature to about 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of an organic or inorganic base such as dimethylaminopyridine, triethylamine, potassium carbonate or cesium carbonate. The methyl ester is then hydrolyzed, for example by treatment with lithium hydroxide in aqueous tetrahydrofuran, to afford the carboxylic acid 29.8. The latter compound is then transformed, by means of the reactions shown in Scheme 3, into the oxirane 29.9.

For example, as illustrated in Scheme 29, Example 1, 4-mercaptophenylalanine 29.10, prepared as described in J. Amer. Chem. Soc., 1997, 119, 7173, is reacted with methanol at reflux temperature in the presence of p-toluenesulfonic acid, to yield the methyl ester 29.11. The thiol substituent is then protected by conversion to the S-adamantyl derivative 29.12, for example by reaction with adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The amino group in the product 29.12 is then protected by conversion to the cbz derivative 29.13, using the procedure described in Scheme 3. Removal of the S-protecting group, for example by treatment of the thioether 29.13 with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, then affords the thiophenol 29.14. The latter compound is then reacted in dimethylformamide solution with a dialkyl bromoalkylphosphonate, for example a dialkyl bromoethylphosphonate 29.15, (Aldrich) in the presence of a base such as cesium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the thioether 29.16. The methyl

ester is then hydrolyzed as described above, and the resultant carboxylic acid **29.17** is transformed, by means of the reactions shown in Scheme 3, into the oxirane **29.18**.

As a further example of the method of Scheme 29, as shown in Example 2, 3-

hydroxyphenylalanine **29.19** (Fluka) is converted into the methyl ester **29.20**, and the phenolic

5 hydroxyl group is then protected by reaction with one molar equivalent of tert-butylchlorodimethylsilane and imidazole in dimethylformamide, as described in J. Amer. Chem. Soc., 94, 6190, 1972, to produce the silyl ether **29.21**. Conversion to the cbz derivative

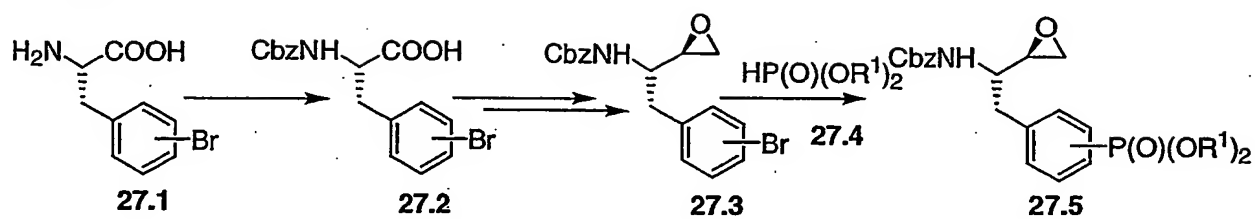
29.22, as described above, followed by desilylation, using tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Amer. Chem. Soc., 94, 6190, 1972, then affords the phenol

10 **29.23**. The phenolic hydroxyl group is then reacted in dimethylformamide solution with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate, **29.24**, prepared as described in Tet. Lett., 1986, 27, 1477, and a base such as triethylamine, to afford the ether **29.25**. The methyl ester is then hydrolyzed, as described above, and the resultant carboxylic acid **29.26** is then transformed, by means of the series of reactions shown in Scheme 3, into the oxirane **29.27**.

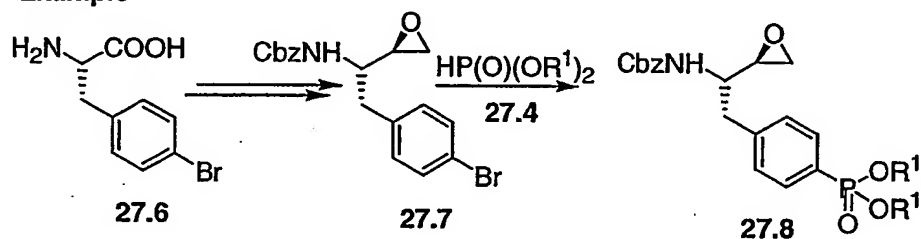
15 Using the above procedures, but employing, in place of the bromoethyl phosphonate **29.15**, or the trifluoromethanesulfonyloxymethyl phosphonate **29.24**, different bromoalkyl or trifluoromethanesulfonyloxyalkyl phosphonates **29.6**, and/or different phenylalanine derivatives **29.1**, the corresponding products **29.9** are obtained.

Scheme 27

Method

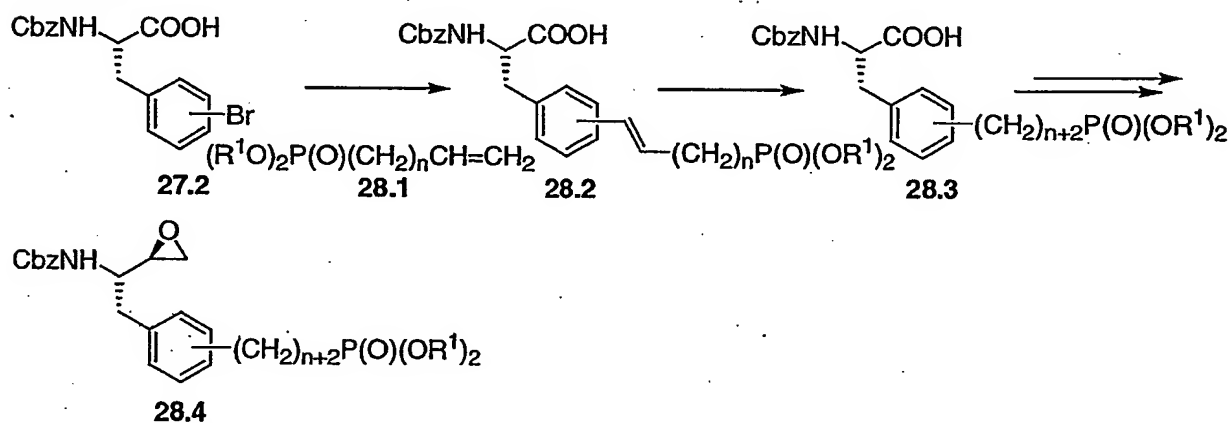


Example

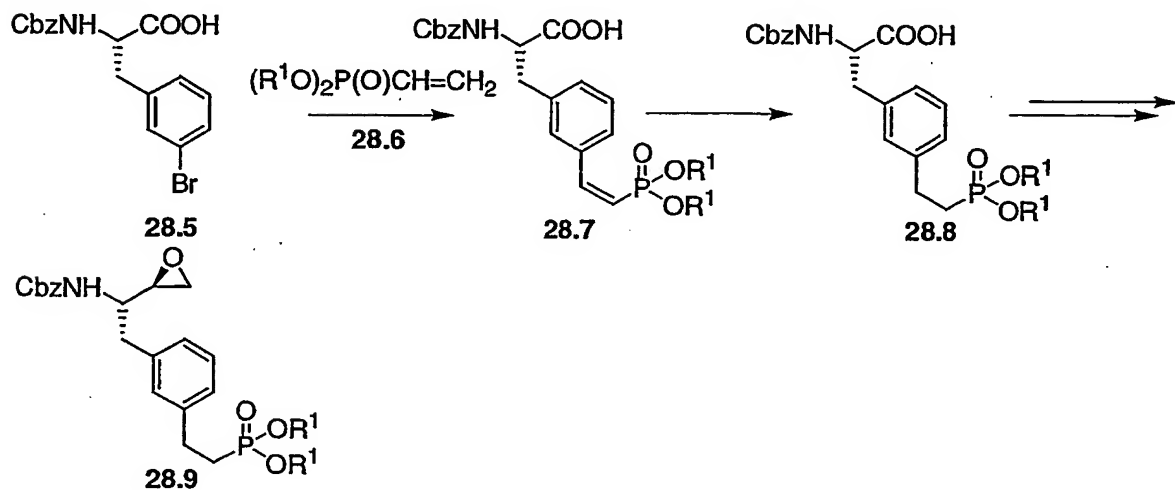


Scheme 28

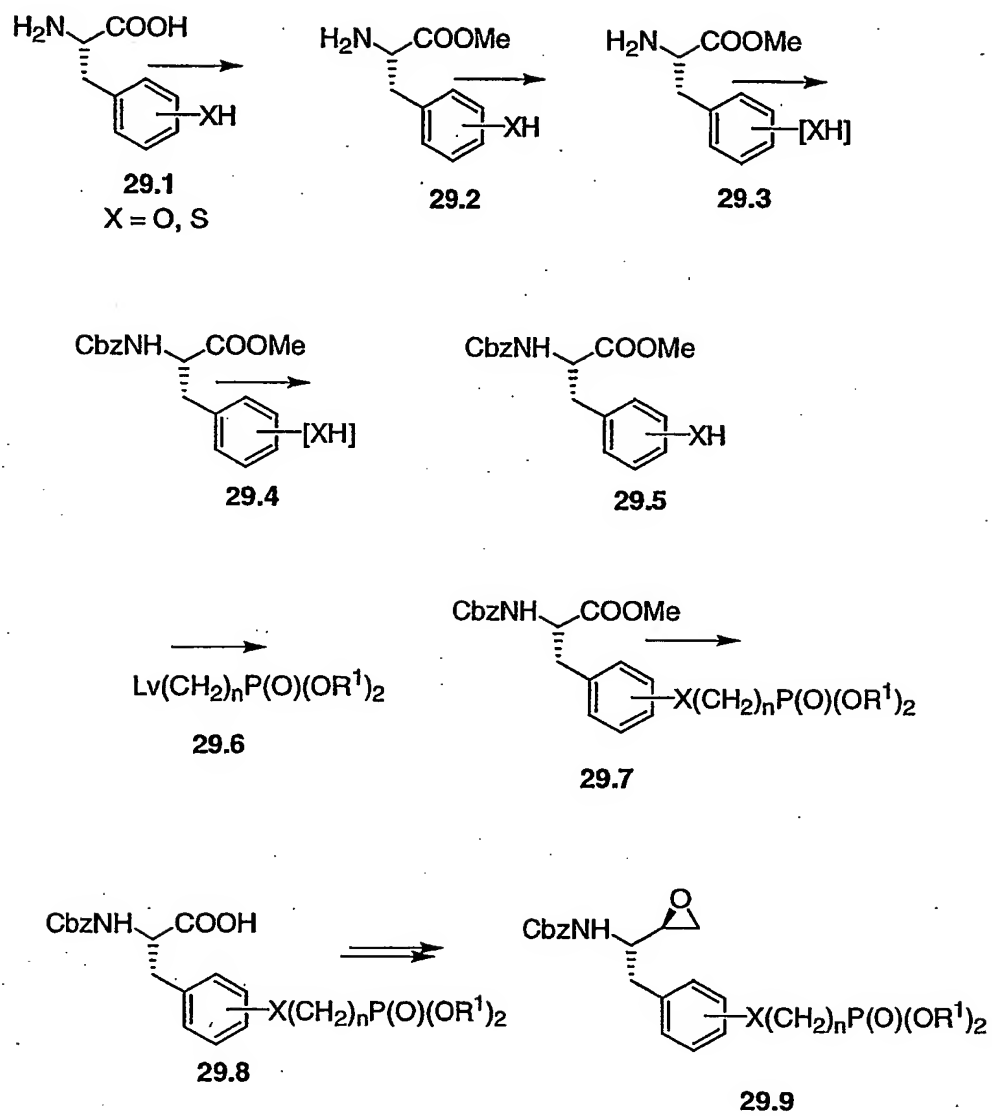
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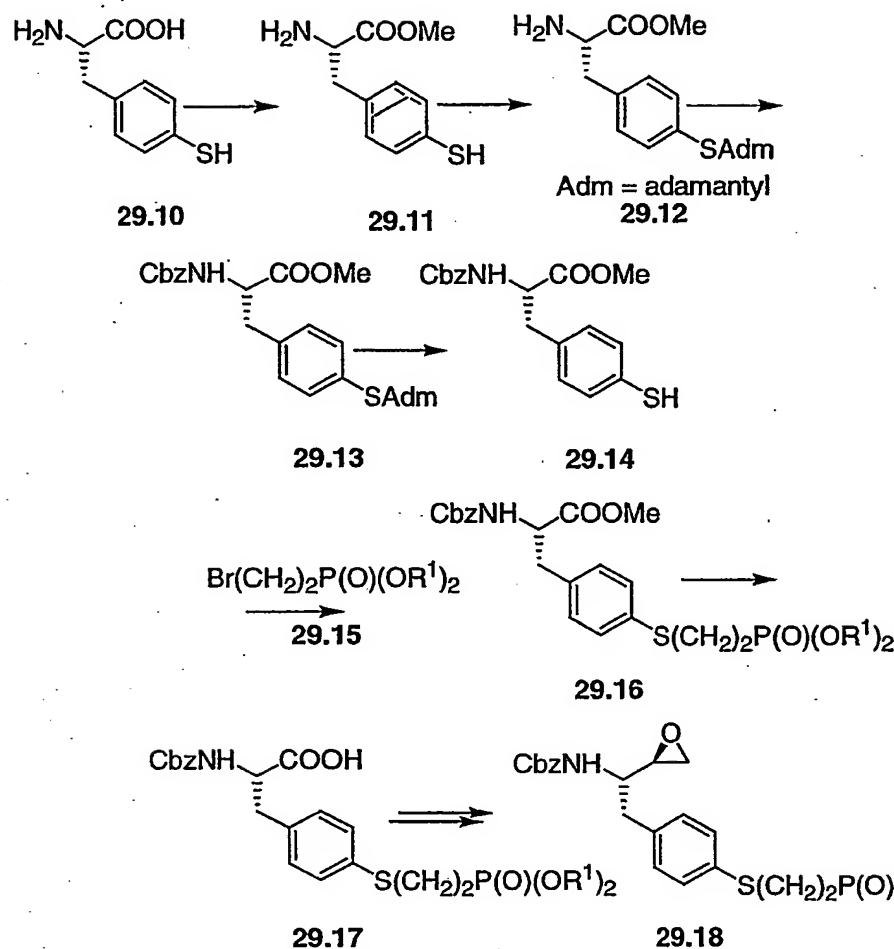
Example



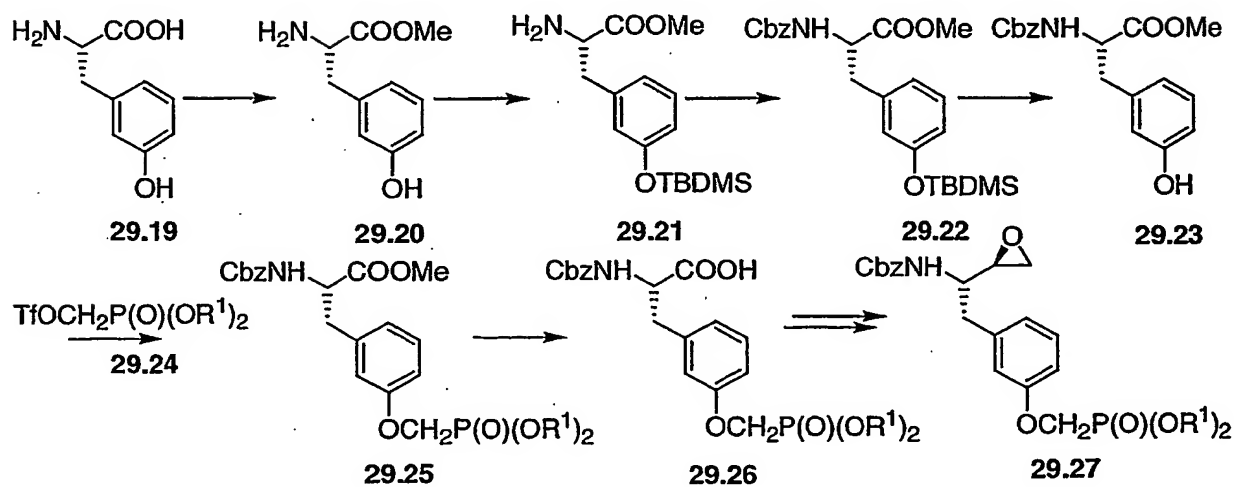
Scheme 29



Example 1



Example 2



Preparation of the phosphonate-containing thiophenol derivatives 10.1.

Schemes 30 - 39 describe the preparation of phosphonate-containing thiophenol derivatives 10.1 which are employed as described above (Schemes 10 and 11) in the preparation of the phosphonate ester intermediates 2.

Scheme 30 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 30.1 is protected, as described above (Scheme 29) to afford the protected product 30.2. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 30.3. The preparation of arylphosphonates by the coupling of aryl halides with dialkyl phosphites is described above, (Scheme 29). The thiol protecting group is then removed, as described above, to afford the thiol 30.4.

For example, 3-bromothiophenol 30.5 is converted into the 9-fluorenylmethyl (Fm) derivative 30.6 by reaction with 9-fluorenylmethyl chloride and diisopropylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 30.3, as described for the preparation of the phosphonate 27.8 (Scheme 27), to afford the phosphonate ester 30.7. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 30.8.

Using the above procedures, but employing, in place of 3-bromothiophenol 30.5, different thiophenols 30.1, and/or different dialkyl phosphites 30.3, the corresponding products 30.4 are obtained.

Scheme 31 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 31.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 31.3. The latter compound is reacted with a halodialkyl phosphite 31.4 to afford the product 31.5; deprotection then affords the thiophenol 31.6.

For example, 4-bromothiophenol 31.7 is converted into the S-triphenylmethyl (trityl) derivative 31.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative **31.9** by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorodialkyl phosphite **31.10** to afford the phosphonate **31.11**. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol **31.12**.
5 Using the above procedures, but employing, in place of the bromo compound **31.7**, different halo compounds **31.2**, and/or different halo dialkyl phosphites **31.4**, there are obtained the corresponding thiols **31.6**.

- 10 Scheme 32 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol is subjected to free-radical bromination to afford a bromomethyl product **32.1**. This compound is reacted with a sodium dialkyl phosphite **32.2** or a trialkyl phosphite, to give the displacement or rearrangement product **32.3**, which upon
15 deprotection affords the thiophenol **32.4**.
For example, 2-methylthiophenol **32.5** is protected by conversion to the benzoyl derivative **32.6**, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product **32.7**. This material is reacted with a sodium dialkyl
20 phosphite **32.2**, as described in J. Med. Chem., 35, 1371, 1992, to afford the product **32.8**. Alternatively, the bromomethyl compound **32.7** can be converted into the phosphonate **32.8** by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound **32.7** is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate **32.8**. Deprotection of the
25 phosphonate **32.8**, for example by treatment with aqueous ammonia, as described in J. Amer. Chem. Soc., 85, 1337, 1963, then affords the thiol **32.9**.
Using the above procedures, but employing, in place of the bromomethyl compound **32.7**, different bromomethyl compounds **32.1**, there are obtained the corresponding thiols **32.4**.

- 30 Scheme 33 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol **33.1** is reacted with a dialkyl hydroxyalkylphosphonate **33.2** under

the conditions of the Mitsunobu reaction, for example as described in *Org. React.*, 1992, 42, 335, to afford the coupled product 33.3. Deprotection then yields the O- or S-linked products 33.4.

- For example, the substrate 3-hydroxythiophenol, 33.5, is converted into the monotrityl ether 33.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 33.7 in benzene, as described in *Synthesis*, 4, 327, 1998, to afford the ether compound 33.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 33.9.
- Using the above procedures, but employing, in place of the phenol 33.5, different phenols or thiophenols 33.1, and different dialkylphosphonates 33.2 there are obtained the corresponding thiols 33.4.

- Scheme 34 illustrates the preparation of thiophenols 34.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 34.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 34.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 34.3. Deprotection then affords the thiol 34.4.

- For example, 4-methylaminothiophenol 34.5 is reacted with one equivalent of acetyl chloride, as described in *Protective Groups in Organic Synthesis*, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the product 34.6. This material is then reacted with, for example, a dialkyl trifluoromethanesulfonylmethyl phosphonate 34.7, the preparation of which is described in *Tet. Lett.*, 1986, 27, 1477, to afford the displacement product 34.8. Preferably, equimolar amounts of the phosphonate 34.7 and the amine 34.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 34.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in *J. Amer. Chem. Soc.*, 85, 1337, 1963, then affords the thiophenol 34.9.

- Using the above procedures, but employing, in place of the thioamine 34.5, different phenols, thiophenols or amines 34.1, and/or different phosphonates 34.2, there are obtained the corresponding products 34.4.

Scheme 35 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 35.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 35.1 is reacted with a dialkyl bromoalkyl phosphonate 35.2 to afford the product 35.3. Deprotection then affords the free thiophenol 35.4.

For example, 3-hydroxythiophenol 35.5 is converted into the S-trityl compound 35.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 35.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, at about 50°, to yield the ether product 35.8. Deprotection, as described above, then affords the thiol 35.9.

Using the above procedures, but employing, in place of the phenol 35.5, different phenols, thiophenols or amines 35.1, and/or different phosphonates 35.2, there are obtained the corresponding products 35.4.

Scheme 36 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 36.2 is coupled with an aromatic bromo compound 36.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 36.4, or the saturated analog 36.6.

For example, 3-bromothiophenol is converted into the S-Fm derivative 36.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 36.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a

palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 36.9. Deprotection, as described above, then affords the thiol 36.10. Optionally, the initially formed unsaturated phosphonate 36.9 is subjected to reduction, for example using diimide, as described above, to yield the saturated product 36.11, which upon deprotection affords the thiol 36.12.

Using the above procedures, but employing, in place of the bromo compound 36.7, different bromo compounds 36.1, and/or different phosphonates 36.2, there are obtained the corresponding products 36.4 and 36.6

Scheme 37 illustrates the preparation of an aryl-linked phosphonate ester 37.4 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid 37.1 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 37.3 which is deprotected to yield the thiol 37.4.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 37.5. This material is reacted with diethyl 4-bromophenylphosphonate 37.6, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product 37.7. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 37.8.

Using the above procedures, but employing, in place of the boronate 37.5, different boronates 37.1, and/or different phosphonates 37.2, there are obtained the corresponding products 37.4.

Scheme 38 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol

38.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 38.2, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 38.3 is then deprotected to afford the thiol 38.4. For example, 1,4-

5 dimercaptobenzene is converted into the monobenzoyl ester 38.5 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 38.5 is then reacted with, for example diethyl 4-(bromomethyl)phenylphosphonate, 38.6, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product 38.7 thus obtained is deprotected, as described
10 above, to afford the thiol 38.8.

Using the above procedures, but employing, in place of the thiophenol 38.5, different phenols, thiophenols or amines 38.1, and/or different phosphonates 38.2, there are obtained the corresponding products 38.4.

15

Scheme 39 illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

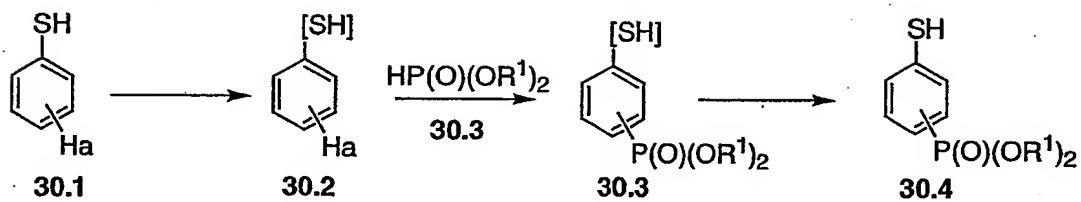
In this procedure, a suitably protected thiophenol 39.1, for example an indoline (in which X-Y is (CH₂)₂), an indole (X-Y is CH=CH) or a tetrahydroquinoline (X-Y is (CH₂)₃) is reacted
20 with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate 39.2, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 39.3. Deprotection, as described above, then affords the thiol 39.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the
25 corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in
30 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived

organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p. 707. For example, 2,3-dihydro-1H-indole-5-thiol, 39.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 39.6, as described above, and the ester is then
5 reacted with the trifluoromethanesulfonate 39.7, using the conditions described above for the preparation of the phosphonate 34.8, (Scheme 34), to yield the phosphonate 39.8. Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol 39.9.

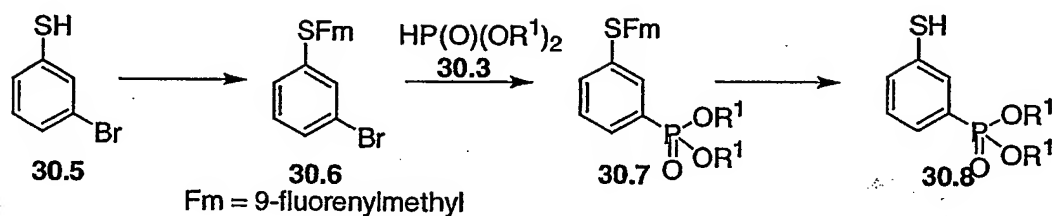
Using the above procedures, but employing, in place of the thiol 39.5, different thiols 39.1,
10 and/or different triflates 39.2, there are obtained the corresponding products 39.4.

Scheme 30

Method

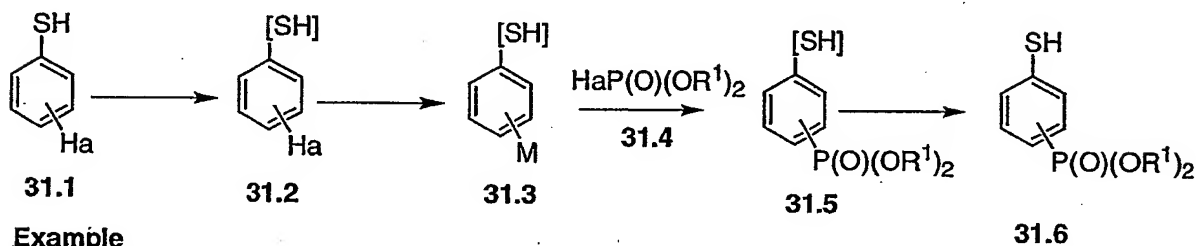


Example

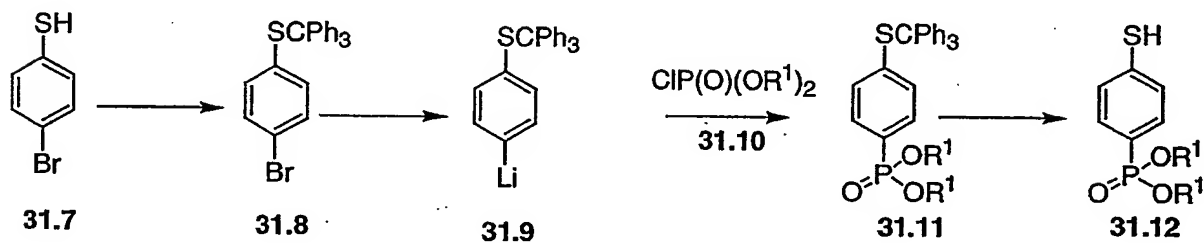


Scheme 31

Method

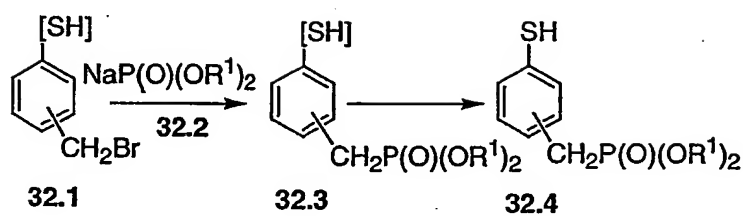


Example

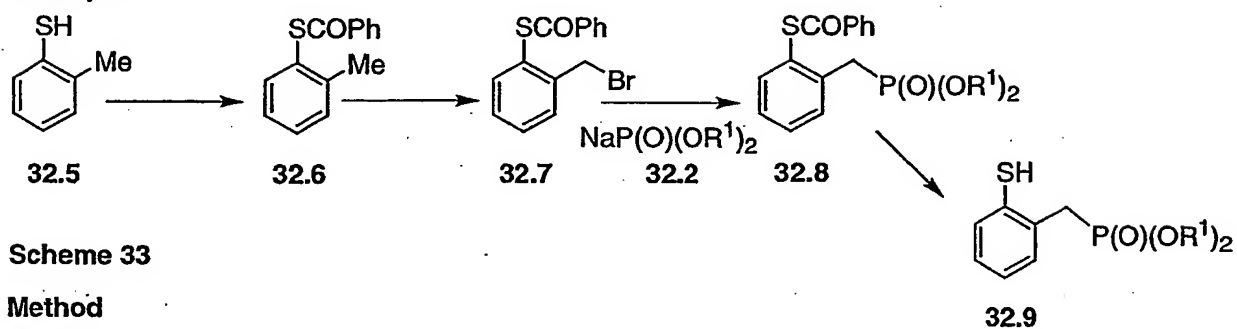


Scheme 32

Method

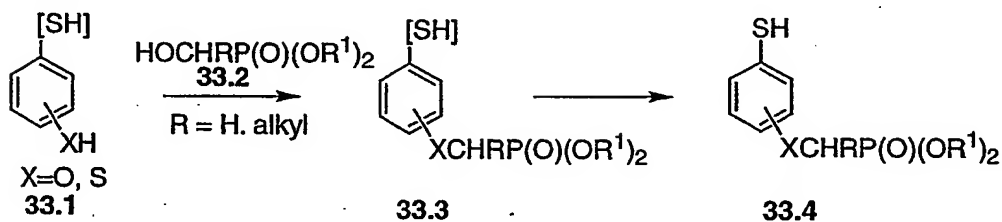


Example

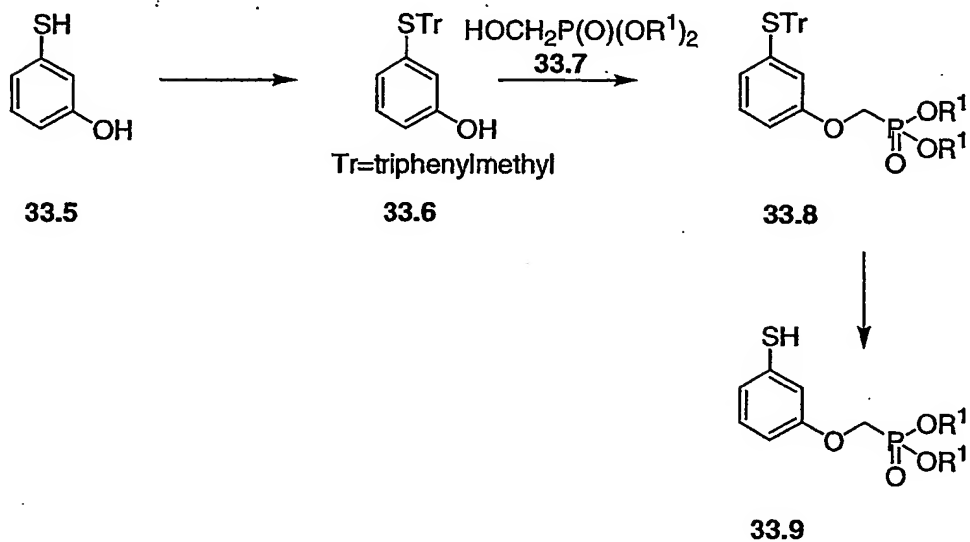


Scheme 33

Method

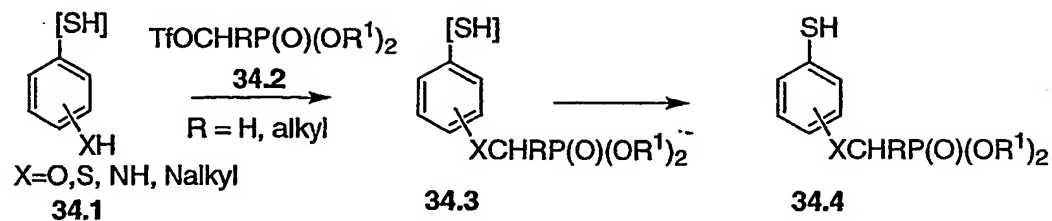


Example

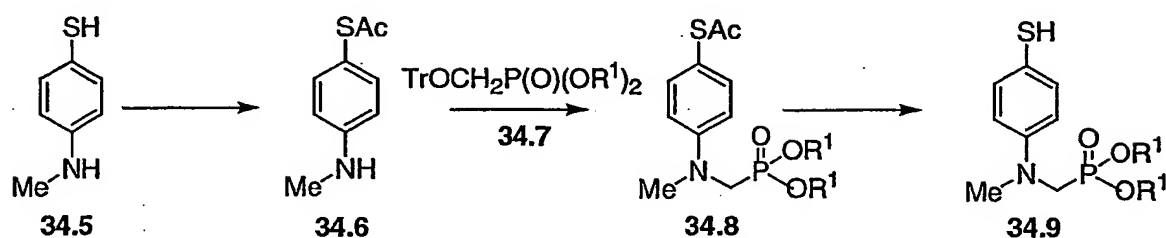


Scheme 34

Method

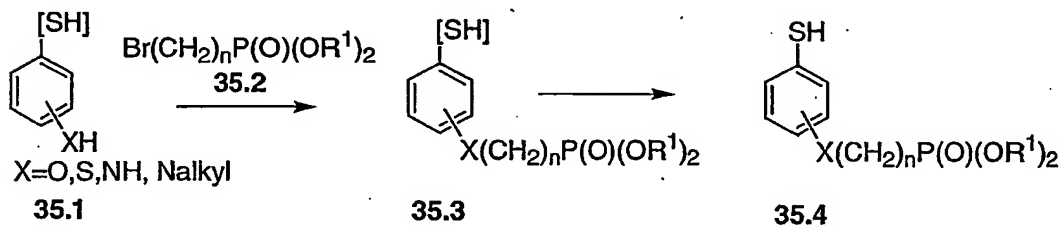


Example

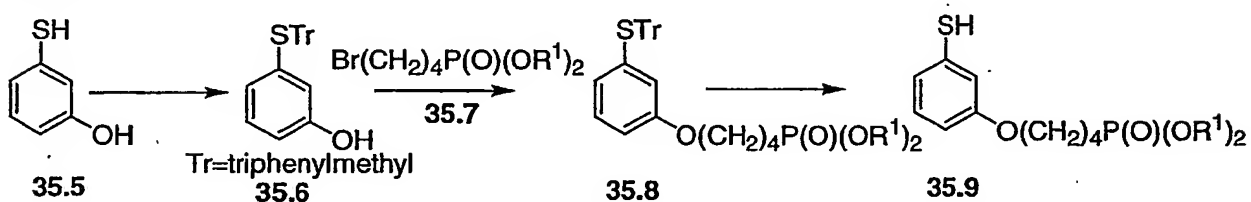


Scheme 35

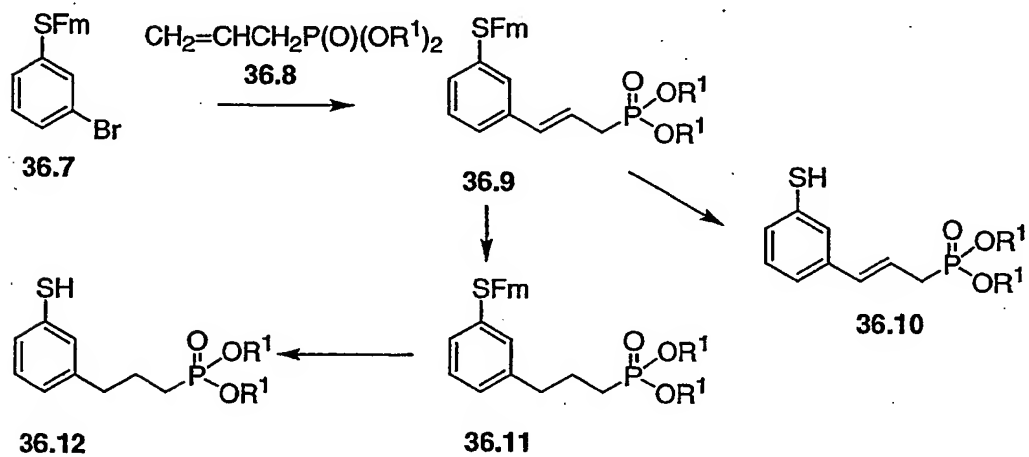
Method



Example

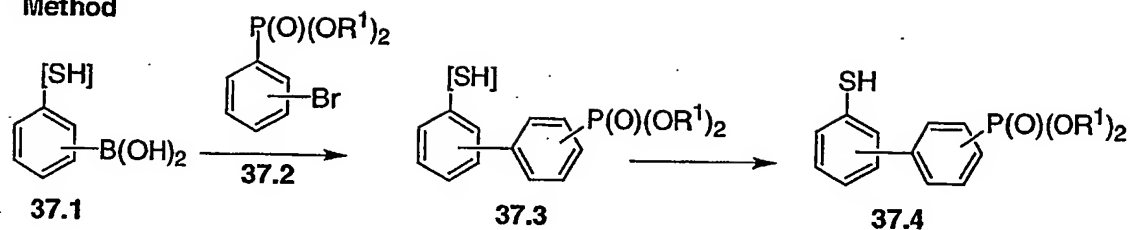


Method

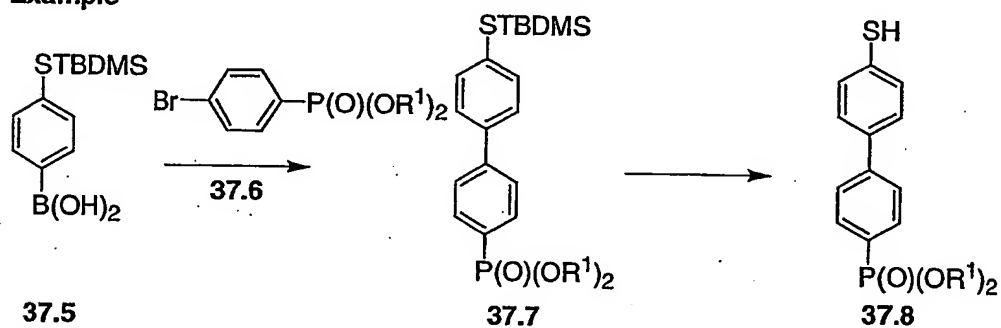


Scheme 37

Method

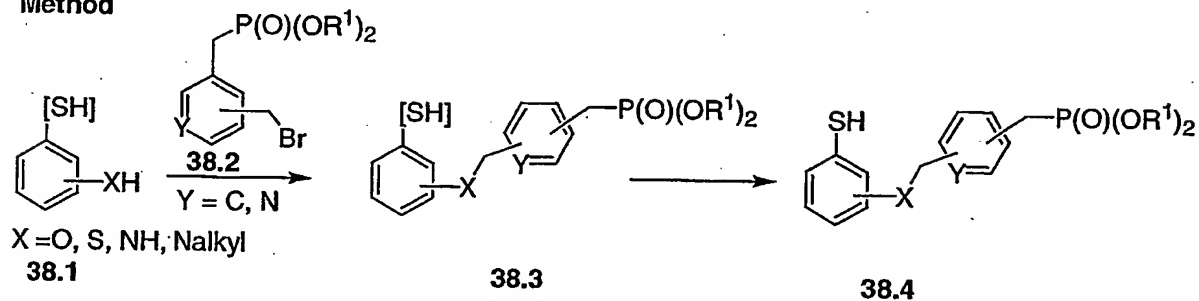


Example

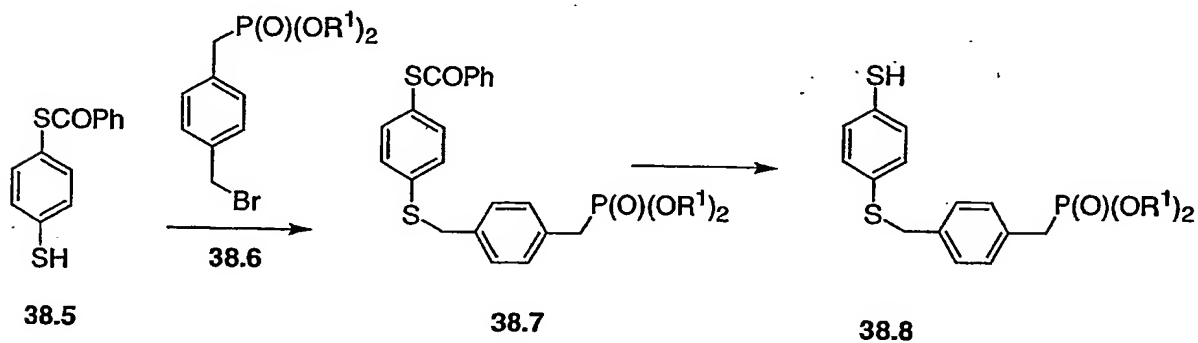


Scheme 38

Method

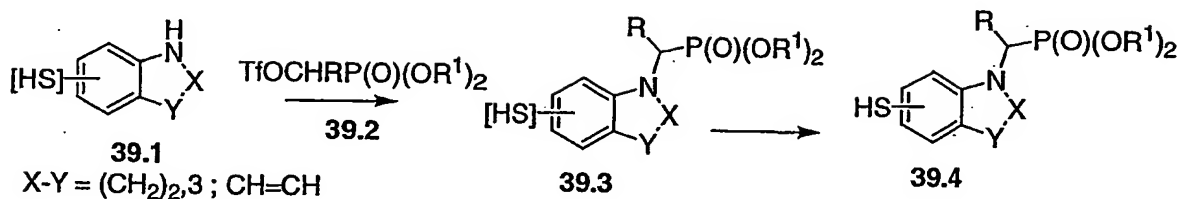


Example

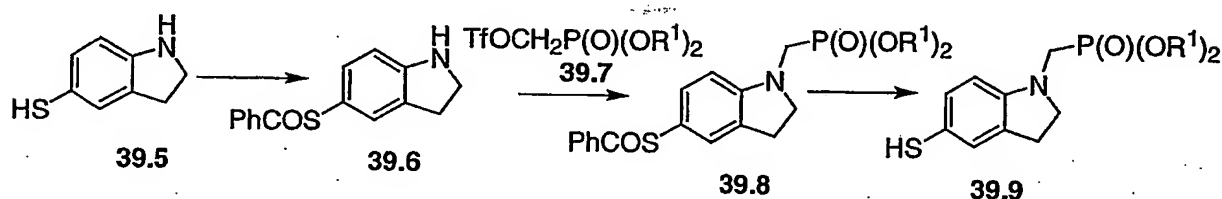


Scheme 39

Method



Example



Preparation of the phenylpyridylphosphonate aldehydes 4.9.

5

Schemes 40 and 41 illustrate methods for the preparation of 4-(2-pyridyl)benzaldehydes 4.9 incorporating phosphonate groups, which are employed in the preparation of the phosphonate ester intermediates 3a.

Scheme 40 illustrates the preparation of benzaldehydes substituted at the 4 position with a bromo-substituted 2-pyridine group, and the conversion of the bromo substituent into various phosphonate substituents, linked to the pyridine ring either directly, or by means of a saturated or unsaturated alkylene chain, or by a heteroatom and an alkylene chain.

In this procedure, a 4-formylphenylboronate **40.1** (Lancaster Synthesis) is coupled with a dibromopyridine **40.2** to afford the bromopyridyl benzaldehyde product **40.3**. Equimolar amounts of the reactants are combined in the presence of a palladium catalyst, as described above (Scheme 4). The bromopyridine product **40.3** is then reacted with a dialkyl phosphite **40.4**, in the presence of a palladium catalyst, as described above (Scheme 27) to afford the pyridylphosphonate ester **40.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992.

20

Alternatively, the bromopyridine compound **40.3** is coupled, in the presence of a palladium catalyst, with a dialkyl alkenylphosphonate **40.6**, to yield the alkenyl phosphonate **40.9**, using

the procedures described above, (Scheme 28). The olefinic bond present in the product is then reduced to afford the saturated analog 40.8. The reduction reaction is performed catalytically, for example by the use of palladium on carbon and hydrogen or a hydrogen donor, or chemically, for example by employing diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961.

Alternatively, the bromopyridine compound 40.3, in which the bromo substituent is in either the 4 or 6 position, is transformed, by reaction with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate 40.7, into the ether, thioether or amine product 40.10. The preparation of pyridine ethers, thioethers and amines by means of displacement reactions of 2- or 4-bromopyridines by alcohols, thiols and amines is described, for example, in Heterocyclic Compounds, Volume 3, R. A. Abramovitch, ed., Wiley, 1975, p. 597, 191, and 41 respectively. Equimolar amounts of the reactants are combined in a polar solvent such as dimethylformamide at ca 100° in the presence of a base such as potassium carbonate, to effect the displacement reaction.

Scheme 40, Example 1, illustrates the coupling reaction of 4-formylphenylboronic acid 40.1 with 2,5-dibromopyridine 40.11, using the procedure described above, to afford 4-(5-bromo-2-pyridyl)benzaldehyde 40.12. This compound is then coupled, as described above, with a dialkyl phosphite 40.4, to afford the pyridyl phosphonate 40.13.

Using the above procedures, but employing, in place of 2,5-dibromopyridine 40.11, different dibromopyridines 40.2, and/or different dialkyl phosphites 40.4, the corresponding products 40.5 are obtained.

Alternatively, as illustrated in Scheme 40, Example 2, the phenylboronic acid 40.1 is coupled, as described above, with 2,4-dibromopyridine 40.14 to afford 4-(4-bromo-2-pyridyl)benzaldehyde 40.15. The product is then reacted with a dialkyl mercaptoethyl phosphonate 40.16, the preparation of which is described in Zh. Obschei. Khim., 1973, 43, 2364, to yield the thioether 40.17. Equimolar amounts of the reactants are combined in dimethylformamide at 80° in the presence of potassium carbonate, to effect the displacement reaction.

Using the above procedures, but employing, in place of the dialkyl mercaptoethyl phosphonate 40.16, different dialkyl hydroxy, mercapto or aminoalkyl phosphonates 40.7, the corresponding products 40.10 are obtained.

Alternatively, as shown in Scheme 40, Example 3, 4-(5-bromo-2-pyridyl)benzaldehyde 40.12 is coupled with a dialkyl vinyl phosphonate 40.18, in the presence of a palladium catalyst, as described above, to afford the unsaturated phosphonate 40.19. Optionally, the product can be reduced to the saturated analog 40.20, for example by the use of diimide, as described above.

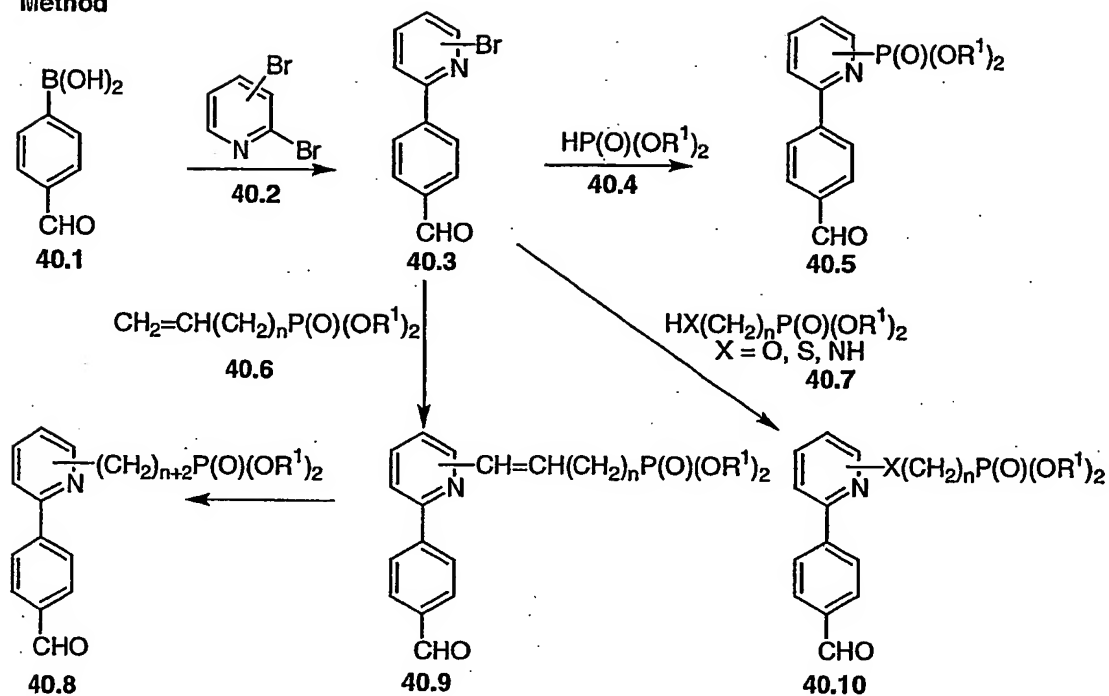
5 Using the above procedures, but employing, in place of the bromoaldehyde 40.12, different bromoaldehydes 40.3, and/or, in place of the dialkyl vinylphosphonate 40.18, different dialkyl alkenylphosphonates 40.6, the corresponding products 40.8 and 40.9 are obtained.

Scheme 41 illustrates the preparation of 4-(2-pyridyl)benzaldehydes incorporating
10 phosphonate group linked by means of a alkylene chain incorporating a nitrogen atom. In this procedure, a formyl-substituted 2-bromopyridine 41.2 is coupled, as described above, (Scheme 40) with a 4-(hydroxymethyl)phenylboronic acid 41.1. prepared as described in Macromolecules, 2001, 34, 3130, to afford the 4-(2-pyridyl)benzyl alcohol 41.3. The product is then reacted with a dialkyl aminoalkyl phosphonate 41.4, under reductive amination
15 conditions. The preparation of amines by means of a reductive amination of an aldehyde is described above (Scheme 24). The resultant benzyl alcohol 41.5 is then oxidized to yield the corresponding benzaldehyde 41.6. The conversion of alcohols to aldehydes is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate,
20 silver carbonate, or dimethyl sulfoxide/acetic anhydride. The reaction is conducted in an inert aprotic solvent such as dichloromethane or toluene. Preferably, the alcohol 41.5 is oxidized to the aldehyde 41.6 by reaction with pyridinium chlorochromate in dichloromethane.

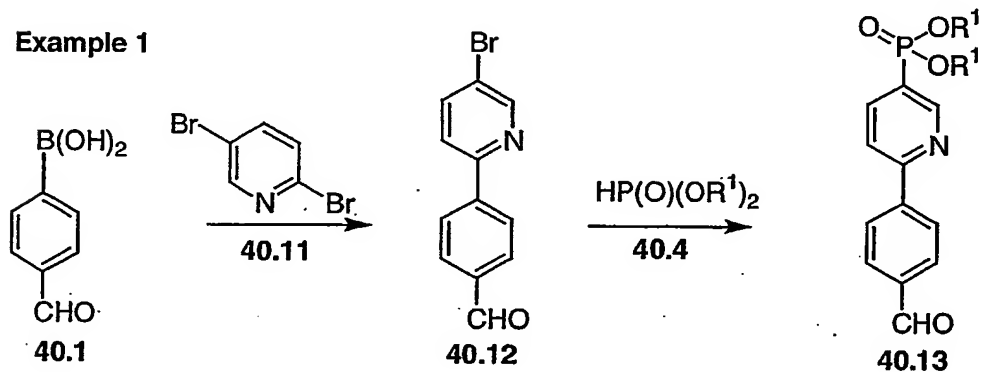
For example, the phenylboronic acid 41.1 is coupled with 2-bromopyridine-4-carboxaldehyde 41.7, the preparation of which is described in Tet. Lett. 2001, 42, 6815, to afford 4-(4-formyl-
25 2-pyridyl)benzyl alcohol 41.8. The aldehyde is then reductively aminated by reaction with a dialkyl aminoethylphosphonate 41.9, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and a reducing agent, to afford the amine product 41.10. The latter compound is then oxidized, for example by treatment with pyridinium chlorochromate, to afford the aldehyde phosphonate 41.11.

30 Using the above procedures, but employing, in place of the bromopyridine aldehyde 41.7, different aldehydes 41.2, and/or different dialkyl aminoalkyl phosphonates 41.4, the corresponding products 41.6 are obtained.

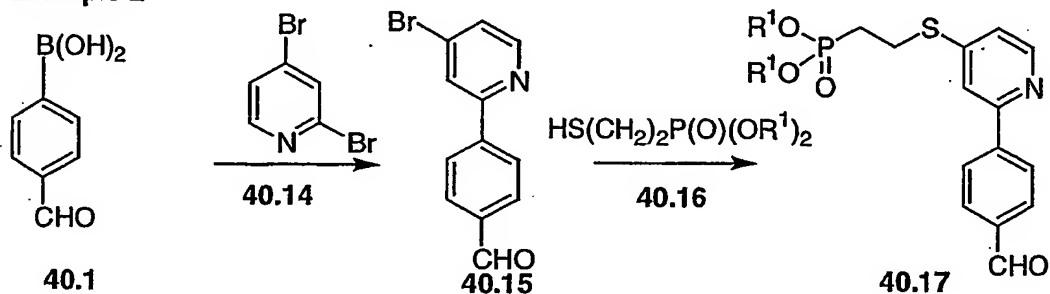
Scheme 40
Method

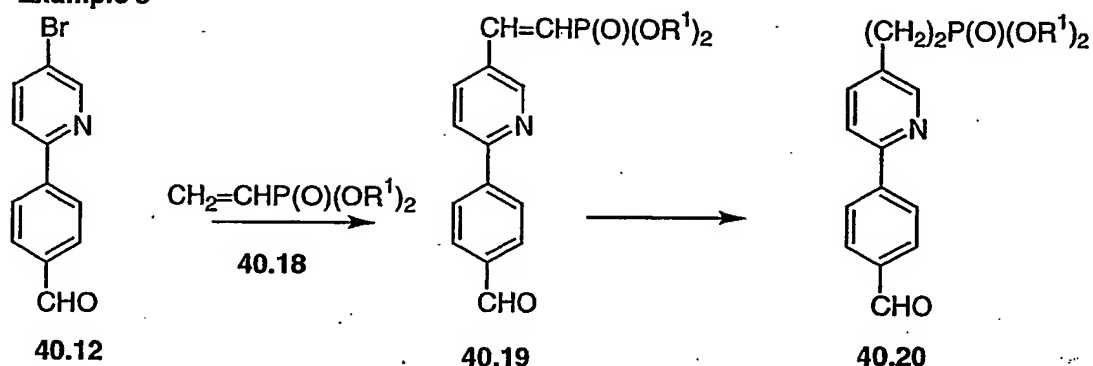
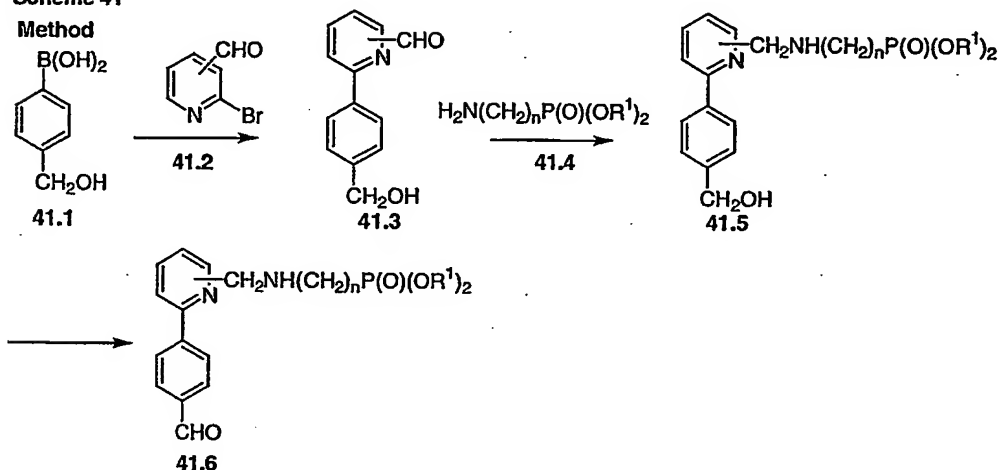
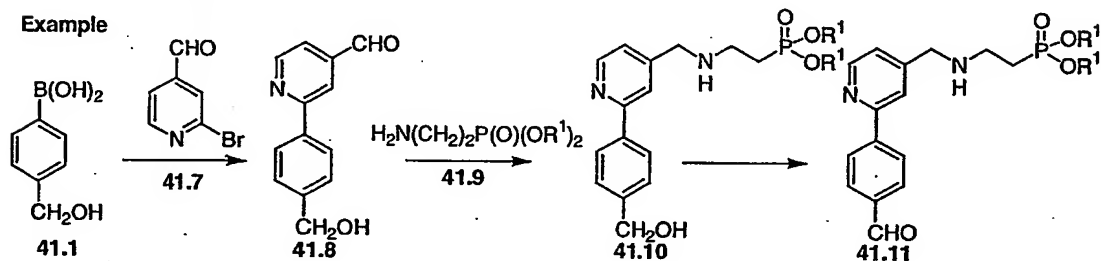


Example 1



Example 2



Example 3**Scheme 41****Method****Example****5 Preparation of the biphenyl phosphonate aldehydes 4.12.**

Schemes 42 - 44 illustrate methods for the preparation of the biphenylphosphonate aldehydes 4.12 which are employed in the synthesis of the phosphonate esters 3b.

Scheme 42 depicts the preparation of biphenyl aldehyde phosphonates in which the phosphonate moiety is attached to the phenyl ring either directly, or by means of a saturated or unsaturated alkylene chain. In this procedure, 4-formylbenzeneboronic acid 42.1 and a

dibromobenzene 42.2 are coupled in the presence of a palladium catalyst, as described above, to produce the bromobiphenyl aldehyde 42.3. The aldehyde is then coupled, as described above, with a dialkyl phosphite 42.4, to afford the phosphonate ester 42.5. Alternatively, the bromoaldehyde 42.3 is coupled with a dialkyl alkenylphosphonate 42.6, using the procedures described above, to afford the alkenyl phosphonate 42.8. Optionally, the latter compound is reduced to yield the saturated analog 42.7.

For example, as shown in Scheme 42, Example 1, 4-formylbenzeneboronic acid 42.1 is coupled with 1,3-dibromobenzene 42.9 to give 3'-bromo-4-formylbiphenyl 42.10. The product is then coupled, as described above, with a dialkyl phosphite 42.4 to give the biphenyl phosphonate ester 42.11.

Using the above procedures, but employing, in place of 1,3-dibromobenzene 42.9, different dibromobenzenes 42.2, and/or different dialkyl phosphites 42.4, the corresponding products 42.5 are obtained.

As a further example of the methods of Scheme 42, as shown in Example 2, 4'-bromobiphenyl-4-aldehyde 42.12 is coupled with a dialkyl propenylphosphonate 42.13 (Aldrich) in the presence of a palladium catalyst, to produce the propenyl phosphonate 42.15. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to yield the saturated product 42.16.

Using the above procedures, but employing, in place of the 4-bromobiphenyl aldehyde 42.12, different bromobiphenyl aldehydes, and/or different alkenyl phosphonates 42.6, the corresponding products 42.7 and 42.8 are obtained.

Scheme 43 illustrates the preparation of biphenyl phosphonates in which the phosphonate group is attached by means of a single carbon or by a heteroatom O, S or N and an alkylene chain. In this procedure, a bromotoluene 43.2 is coupled with 4-formylbenzeneboronic acid 43.1 to yield the methyl-substituted biphenyl aldehyde 43.3. The product is then subjected to a free radical bromination to produce the bromomethyl compound 43.4. The conversion of aromatic methyl groups into the corresponding benzylic bromide is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 313. The transformation is effected, for example, by the use of bromine, N-bromosuccinimide, carbon tetrabromide or bromotrichloromethane. The reaction is performed in an inert organic solvent such as carbon tetrachloride, ethyl acetate and the like, at reflux temperature, optionally in the

presence of an initiator such as dibenzoyl peroxide. Preferably, the conversion of the methyl compound 43.3 to the bromomethyl product 43.4 is effected by the use of one molar equivalent of N-bromosuccinimide in refluxing carbon tetrachloride. The bromomethyl compound is then reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate product 43.6. The displacement reaction is performed in an inert solvent such as tetrahydrofuran, at from ambient temperature to reflux, as described in J. Med. Chem., 1992, 35, 1371.

Alternatively, the bromomethyl compound 43.4 is reacted with a dialkyl hydroxy, mercapto or aminoalkyl phosphonate 43.7 to prepare the corresponding ether, thioether or aminoalkyl phosphonate products 43.8. The reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, at from ambient temperature to about 80°, in the presence of an inorganic or organic base. For the preparation of the ethers 43.8 in which X is O, a strong base such as sodium hydride or potassium tert. butoxide is employed. For the preparation of the thioethers or amines 43.8, a base such as cesium carbonate, dimethylaminopyridine or diisopropylethylamine is employed.

Scheme 43, Example 1 depicts the coupling reaction of 4-formylbenzeneboronic acid 43.1 with 3-bromotoluene 43.9 to afford 3'-methylbiphenyl-4-aldehyde 43.10. The product is then reacted with N-bromosuccinimide, as described above, to afford the bromomethyl product 43.11. This material is reacted with a sodium dialkyl phosphonate 43.5 to afford the phosphonate ester 43.12.

Using the above procedures, but employing, in place of 3-bromotoluene 43.9, different bromotoluenes 43.2, the corresponding products 43.6 are obtained.

Scheme 43, Example 2 shows the free-radical bromination of 4'-methylbiphenyl-4-aldehyde to give the 4'-bromomethylbiphenyl-4-aldehyde 43.14. The product is then reacted in acetonitrile solution at 70° with one molar equivalent of a dialkyl aminoethyl phosphonate 43.15, the preparation of which is described in J. Org. Chem., 2000, 65, 676, and cesium carbonate, to yield the amine product 43.16.

Using the above procedures, but employing, in place of the aminoethyl phosphonate 43.15, different hydroxy, mercapto or aminoalkyl phosphonates 43.7, and/or different biphenyl aldehydes 43.3, the corresponding products 43.8 are obtained.

Scheme 44 illustrates the preparation of the biphenyl phosphonates 44.3 in which the phosphonate group is attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted biphenyl aldehyde 44.1 is reacted with a dialkyl bromoalkyl phosphonate 44.2 to afford the alkylation product 44.3. The reaction is conducted between equimolar amounts of the reactants in a polar organic solvent such as dimethylformamide and the like, at from ambient temperature to about 80°, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of an inorganic iodide such as potassium iodide.

For example, 3'-hydroxybiphenyl-4-aldehyde 44.4 is reacted with a dialkyl bromoethyl phosphonate 44.5 (Aldrich) and potassium carbonate in dimethylformamide at 80°, to produce the ether 44.6.

Using the above procedures, but employing, in place of 3'-hydroxybiphenyl-4-aldehyde 44.4, different hydroxy, mercapto or aminobiphenyl-4-aldehydes 44.1, and/or different bromoalkyl phosphonates 44.2, the corresponding products 44.3 are obtained.

Preparation of the benzaldehyde phosphonates 4.14.

Schemes 45 - 48 illustrate methods for the preparation of the benzaldehyde phosphonates 4.14 which are employed in the synthesis of the phosphonate esters 3d.

Scheme 45 illustrates the preparation of benzaldehyde phosphonates 45.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 45.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 45.2, under reductive amination conditions, as describe above in Scheme 24, to yield the phosphonate product 45.3.

For example, benzene-1,3-dialdehyde 45.4 is reacted with a dialkyl aminopropyl phosphonate 45.5, (Acros) and sodium triacetoxyborohydride, to afford the product 45.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 45.4, different benzene dialdehydes 45.1, and/or different phosphonates 45.2, the corresponding products 45.3 are obtained.

Scheme 46 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this

procedure, a bromobenzaldehyde 46.1 is coupled, under palladium catalysis as described above, with a dialkyl alkenylphosphonate 46.2, to afford the alkenyl phosphonate 46.3. Optionally, the product can be reduced, as described above, to afford the saturated phosphonate ester 46.4. Alternatively, the bromobenzaldehyde can be coupled, as described

5 above, with a dialkyl phosphite 46.5 to afford the formylphenylphosphonate 46.6.

For example, as shown in Example 1, 3-bromobenzaldehyde 46.7 is coupled with a dialkyl propenylphosphonate 46.8 to afford the propenyl product 46.9. Optionally, the product is reduced to yield the propyl phosphonate 46.10.

Using the above procedures, but employing, in place of 3-bromobenzaldehyde 46.7, different

10 bromobenzaldehydes 46.1, and/or different alkenyl phosphonates 46.2, the corresponding products 46.3 and 46.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde 46.11 is coupled with a dialkyl phosphite 46.5 to afford the 4-formylphenyl phosphonate product 46.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 46.11, different

15 bromobenzaldehydes 46.1, the corresponding products 46.6 are obtained.

Scheme 47 illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or

20 alkylamine 47.1 is reacted with a an equimolar amount of a dialkyl haloalkyl phosphonate 47.2, to afford the phenoxy, phenylthio or phenylamino phosphonate product 47.3. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 47.1. In cases in which Y is O, a strong base such as sodium hydride or lithium

25 hexamethyldisilazide is employed. In cases in which Y is O or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol 47.4, prepared as described in *Macromolecules*, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate 47.5, (Lancaster) to give the ether product 47.6.

Using the above procedures, but employing, in place of the carbinol 47.4, different carbinols, thiols or amines 47.1, and/or different haloalkyl phosphonates 47.2, the corresponding

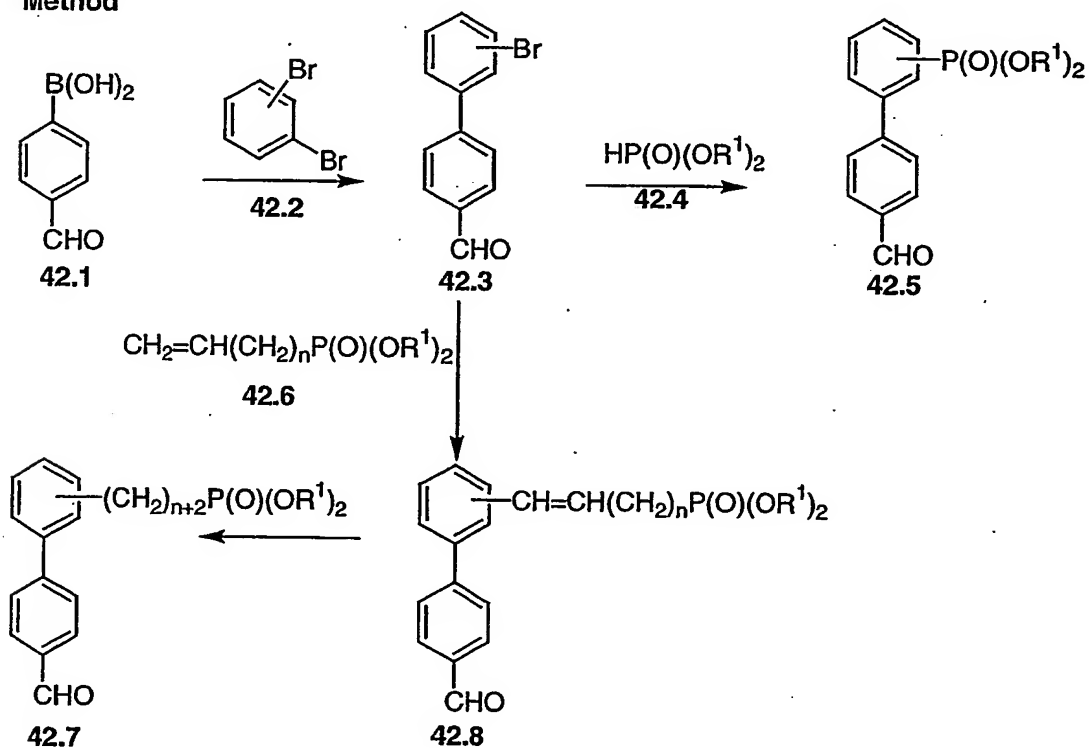
30 products 47.3 are obtained.

Scheme 48 illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, 4-formylbenzeneboronic acid 43.1 is coupled, as described previously, with one molar equivalent of a dibromoarene, 48.1, in which the group Ar is an aromatic or heteroaromatic group. The product 48.2 is then coupled, as described above (Scheme 46) with a dialkyl phosphite 40.4 to afford the phosphonate 48.3.

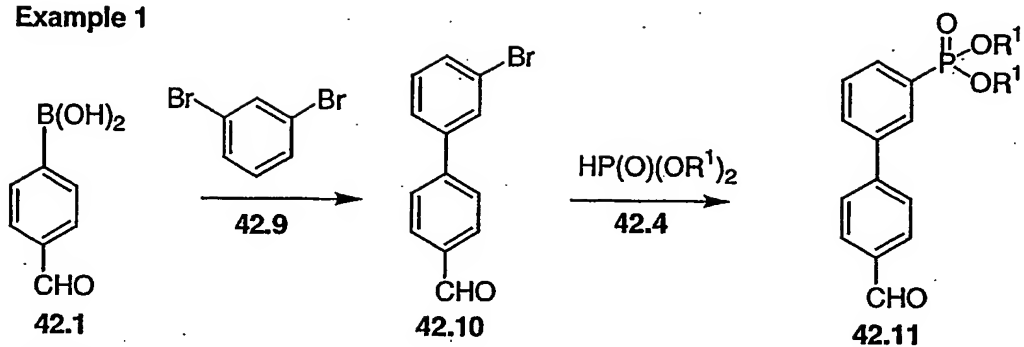
For example, 4-formylbenzeneboronic acid 43.1 is coupled with 2,5-dibromothiophene 48.4 to yield the phenylthiophene product 48.5. This compound is then coupled with the dialkyl phosphite 40.4 to afford the thienyl phosphonate 48.6.

Using the above procedures, but employing, in place of dibromothiophene 48.4, different dibromoarenes 48.1, the corresponding products 48.3 are obtained.

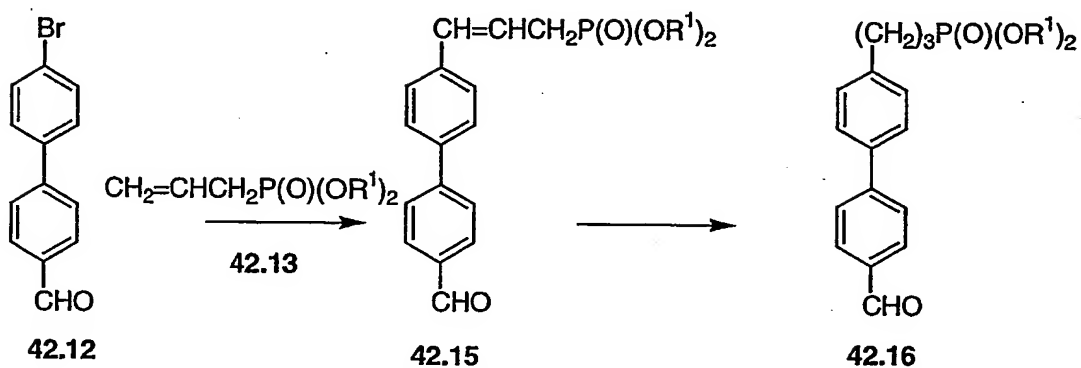
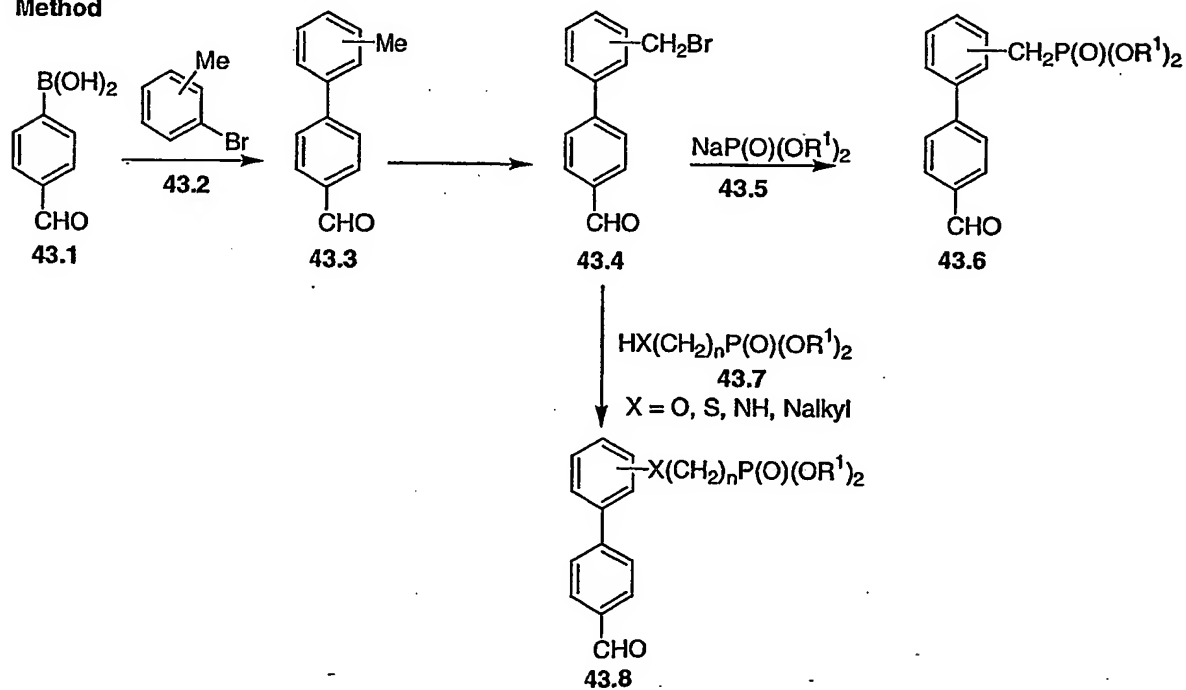
Scheme 42
Method



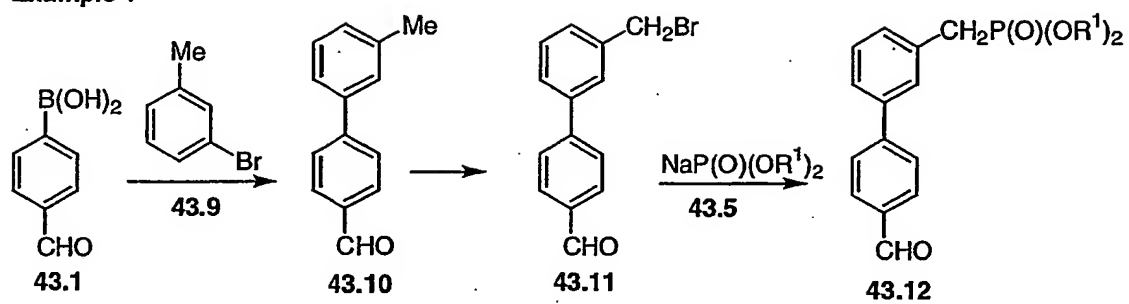
Example 1



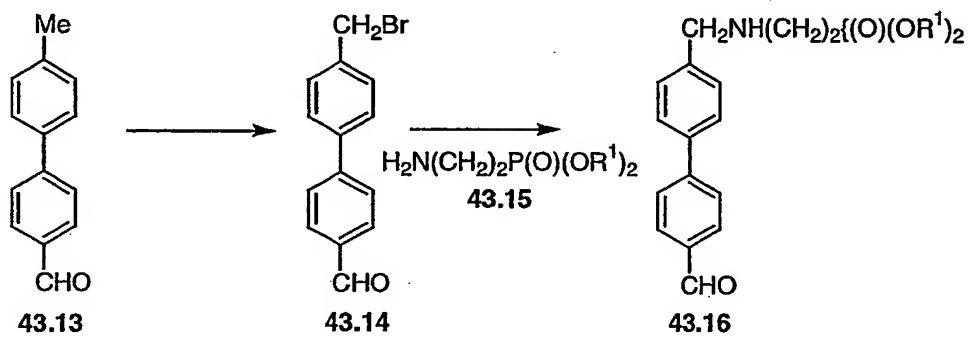
Example 2

Scheme 43
Method

Example 1

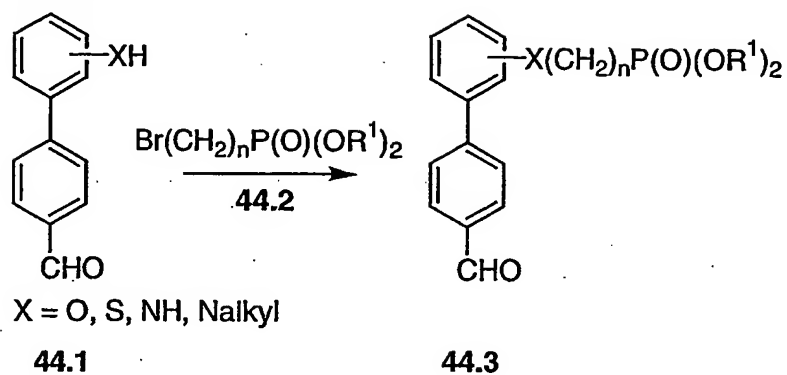


Example 2

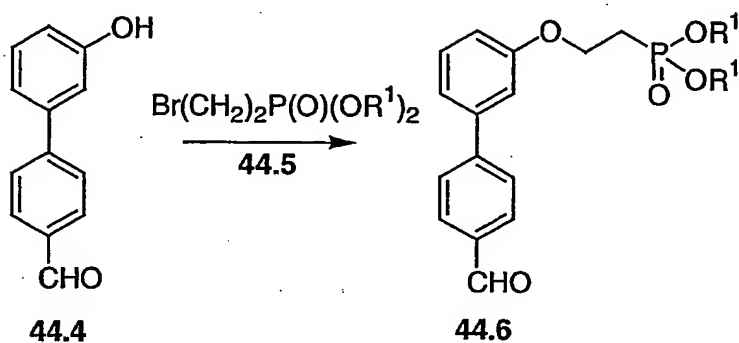


Scheme 44

Method

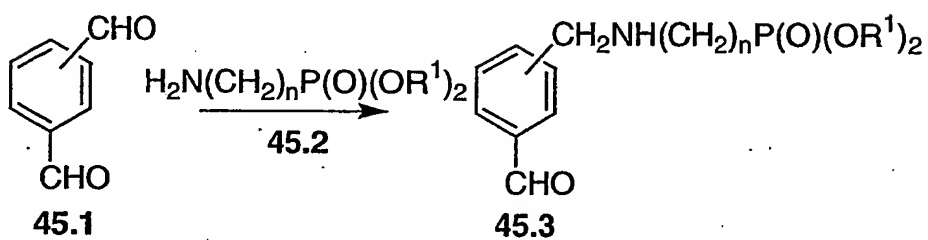


Example

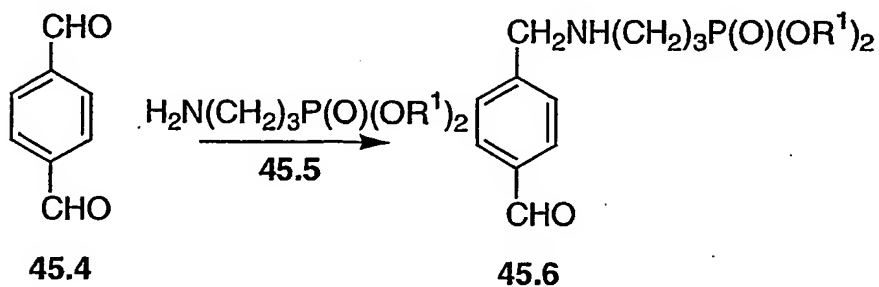


Scheme 45

Method

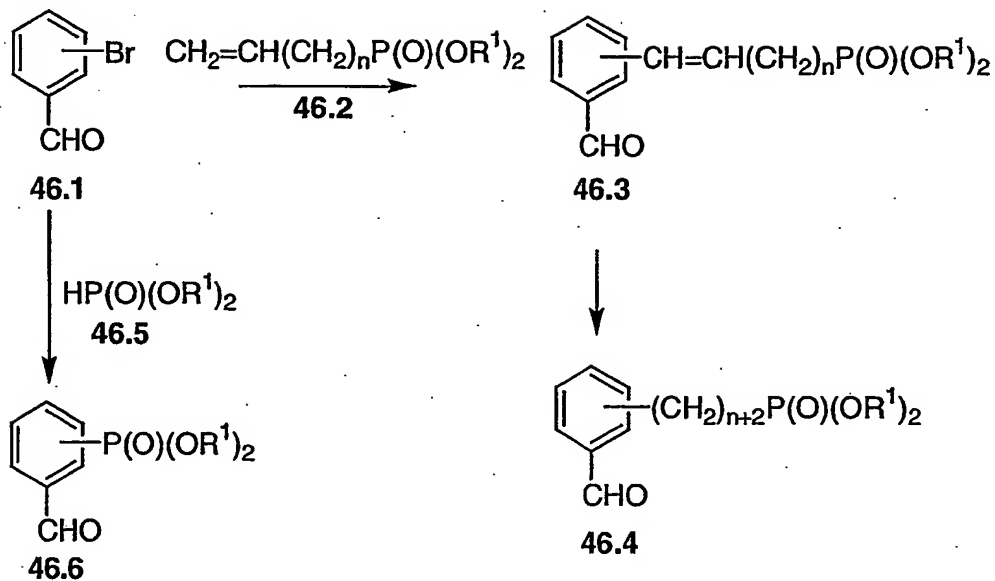


Example

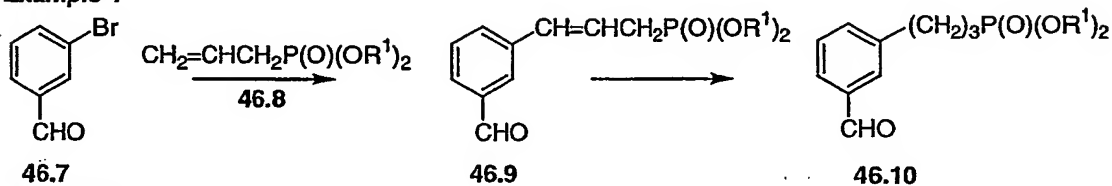


Scheme 46

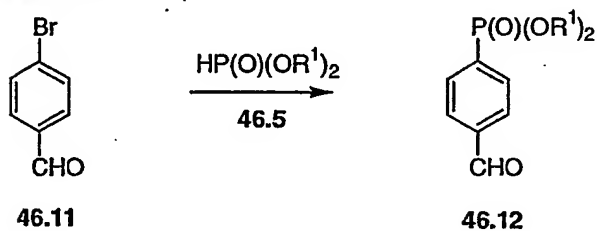
Method



Example 1

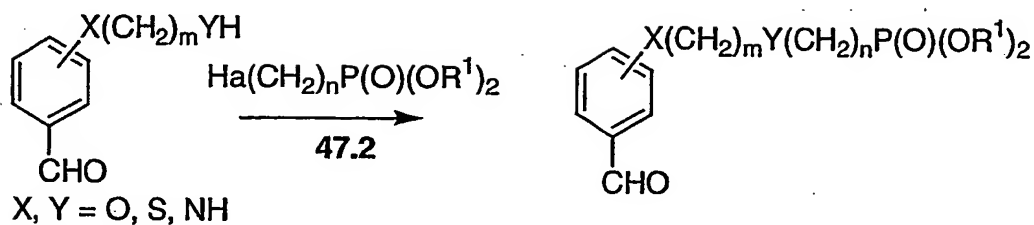


Example 2



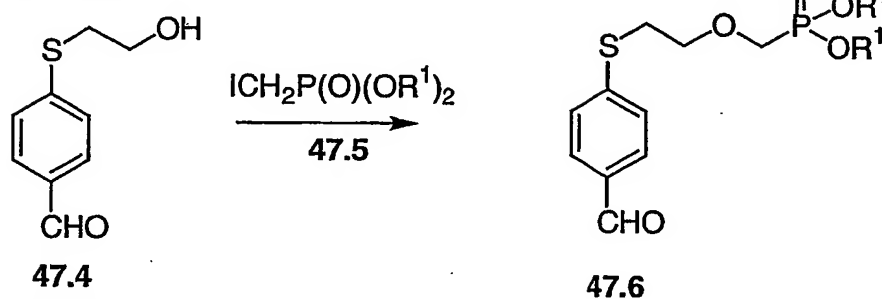
Scheme 47

Method



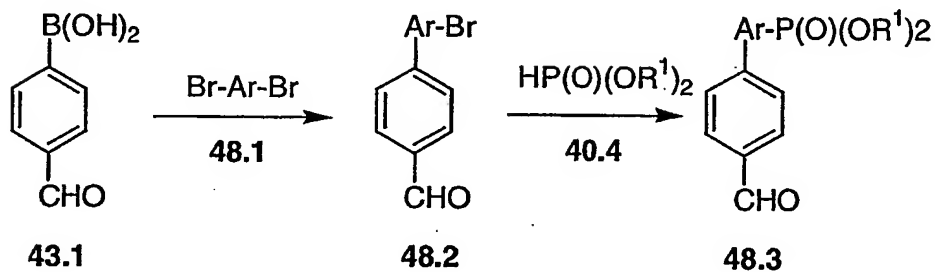
47.1

Example

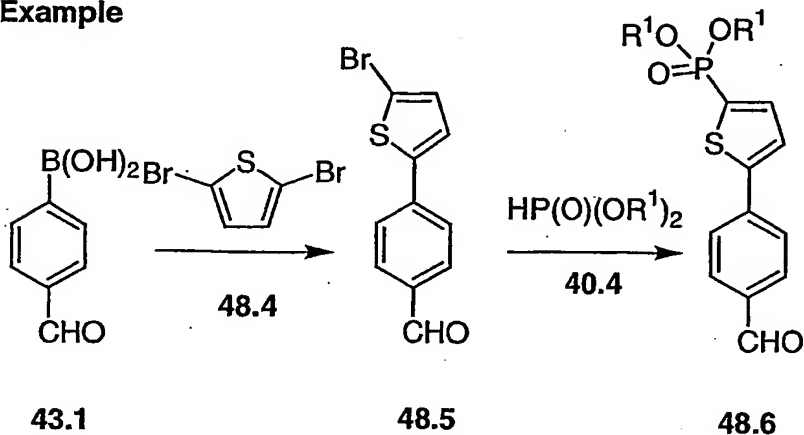


Scheme 48

Method



Example



Preparation of the cyclohexanecarboxaldehyde phosphonates 4.16.

Schemes 49 - 52 illustrate methods for the preparation of the cyclohexanecarboxaldehyde phosphonates 4.16 which are employed in the synthesis of the phosphonate esters 3c.
Scheme 49 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a nitrogen and an alkylene chain. In this procedure, a cyclohexane dicarboxaldehyde 49.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 49.2 under reductive amination conditions, as described above, to afford the phosphonate product 49.3.

For example, cyclohexane-1,3-dialdehyde 49.4, the preparation of which is described in J. Macromol. Sci. Chem., 1971, 5, 1873, is reacted with a dialkyl aminopropyl phosphonate 49.5, (Acros) and one molar equivalent of sodium triacetoxyborohydride, to yield the phosphonate product 49.6.
Using the above procedures, but employing, in place of cyclohexane-1,3-dialdehyde 49.4, different cyclohexane dialdehydes 49.1, and /or different aminoalkyl phosphonates 49.2, the corresponding products 49.3 are obtained.

Scheme 50 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of a vinyl or ethylene group and a phenyl ring. In this procedure, a vinyl-substituted cyclohexane carboxaldehyde 50.1 is coupled, in the presence of a palladium catalyst, as described above, (Scheme 36) with a dialkyl bromophenylphosphonate 50.2, to afford the phosphonate product 50.3. Optionally, the product is reduced to afford the ethylene-linked analog 50.4. The reduction reaction is effected catalytically, for example by the use of hydrogen in the presence of a palladium catalyst, or chemically, for example by the use of diimide.

For example, 4-vinylcyclohexanecarboxaldehyde 50.5, the preparation of which is described in WO 9935822, is coupled with a dialkyl 3-bromophenyl phosphonate 50.6, prepared as described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, to give the coupled product 50.7. The product is then reduced with diimide, generated by treatment of disodium azodicarboxylate with acetic acid, as described in J. Am. Chem. Soc., 83, 3725, 1961, to yield the saturated product 50.8.

Using the above procedures, but employing, in place of 4-vinylcyclohexanecarboxaldehyde 50.5, different vinylcyclohexane carboxaldehydes 50.1, and /or different bromophenyl phosphonates 50.2, the corresponding products 50.3 and 50.4 are obtained.

5 Scheme 51 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is attached by means of an alkylene chain incorporating an oxygen atom. In this procedure, a hydroxymethyl-substituted cyclohexane carboxaldehyde 51.1 is reacted, in the presence of a strong base such as sodium hydride or potassium tert. butoxide, with one molar equivalent of a dialkyl bromoalkyl phosphonate 51.2, to prepare the phosphonate 51.3. The
10 alkylation reaction is conducted in a polar organic solvent such as dimethylformamide, tetrahydrofuran or acetonitrile, at from ambient temperature to about 60°.

For example, 3-(hydroxymethyl)cyclohexanecarboxaldehyde 51.4, prepared as described in WO 0107382, is treated with one molar equivalent of sodium hydride in tetrahydrofuran at 50°, and one molar equivalent of a dialkyl bromoethyl phosphonate 51.5 (Aldrich) to afford
15 the alkylation product 51.6.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)cyclohexanecarboxaldehyde 51.4 different hydroxymethylcyclohexane carboxaldehydes 51.1, and /or different bromoalkyl phosphonates 51.2, the corresponding
20 products 51.3 are obtained.

Scheme 52 depicts the preparation of cyclohexyl phosphonates in which the phosphonate group is directly attached to the cyclohexane ring. In this procedure, a hydroxy-substituted cyclohexanecarboxaldehyde 52.1 is converted into the corresponding bromo derivative 52.2. The conversion of alcohols into the corresponding bromides is described, for example, in
25 Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 354ff and p. 356ff. The transformation is effected by treatment of the alcohol with hydrobromic acid, or by reaction with hexabromoethane and triphenylphosphine, as described in Synthesis, 139, 1983. The resulting bromo compound 52.2 is then subjected to an Arbuzov reaction, by treatment with a trialkyl phosphite 52.3 at ca 100°. The preparation of phosphonates by mean of the
30 Arbuzov reaction is described in Handb. Organophosphorus Chem., 1992, 115.

For example, 4-hydroxycyclohexanecarboxaldehyde 52.5 is reacted with one molar equivalent of hexabromoethane and triphenyl phosphine in dichloromethane, to yield 4-

bromocyclohexanecarboxaldehyde 52.6. The product is heated at 100° with a trialkyl phosphite 52.3 to afford the cyclohexyl phosphonate 52.7.

Using the above procedures, but employing, in place of 4-

(hydroxymethyl)cyclohexanecarboxaldehyde 52.5, different hydroxy-substituted

5 cyclohexanecarboxaldehydes 52.1, the corresponding products 52.4 are obtained.

Preparation of quinoline 2-carboxylic acids 19a.1 incorporating phosphonate moieties or precursors thereto.

10 The reaction sequence depicted in Schemes 19a - 19d require the use of a quinoline-2-carboxylic acid reactant 19a.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br.

A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino
15 and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described,
20 for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

25 Scheme 53 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 53.1 is reacted with an alkyl pyruvate ester 53.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 53.3. Hydrolysis of the ester, for example by the use of aqueous base, then
30 afford the corresponding carboxylic acid 53.4. The carboxylic acid product 53.4 in which X is NH₂ can be further transformed into the corresponding compounds 53.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The

conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the
5 diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol 53.6, X = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic
10 Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, 53.6, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 200, 24, 123, to afford the thiol 53.6, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters 53.3 instead
15 of the carboxylic acids 53.5.

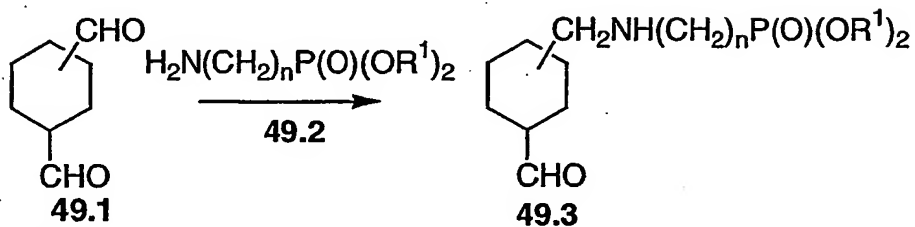
For example, 2,4-diaminobenzaldehyde 53.7 (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate 53.2 in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate 53.8. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the
20 carboxylic acid 53.9. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate 53.10 by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, 53.11, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-
25 bromoquinoline-2-carboxylic acid 53.11, X = Br. Alternatively, the diazonium tetrafluoroborate 53.10 is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid 53.11, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 53.7,
30 different aminobenzaldehydes 53.1, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids 53.6 are obtained. The variously substituted quinoline

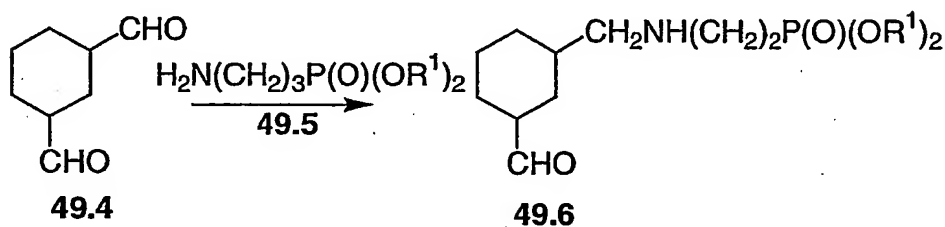
carboxylic acids and esters can then be transformed, as described below, (Schemes 54 – 56) into phosphonate-containing derivatives.

Scheme 49

Method



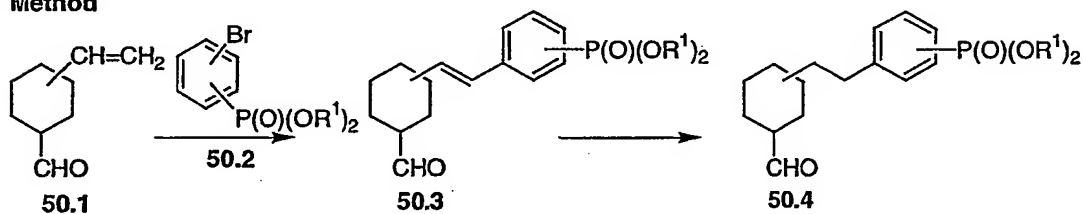
Example



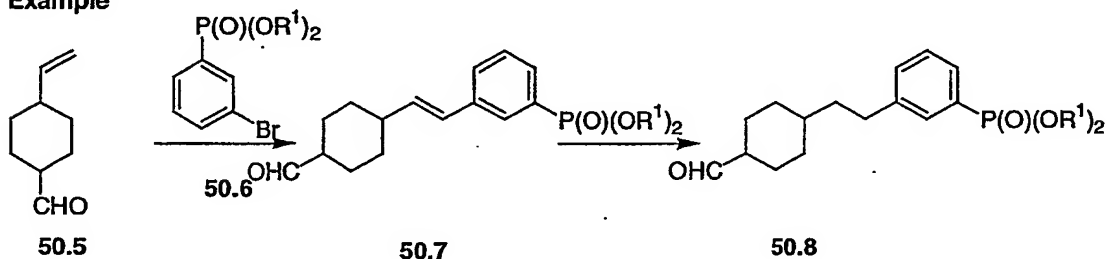
5

Scheme 50

Method

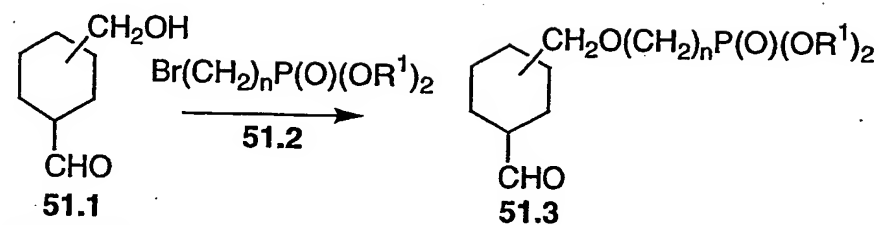


Example

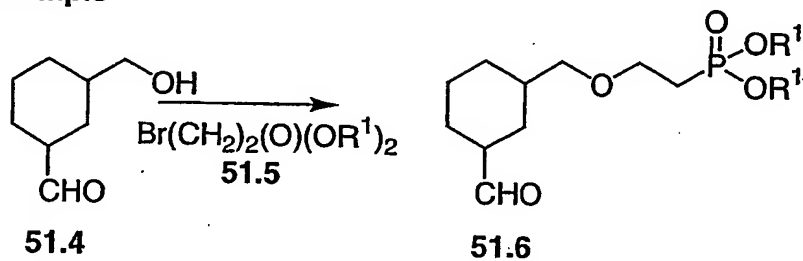


Scheme 51

Method

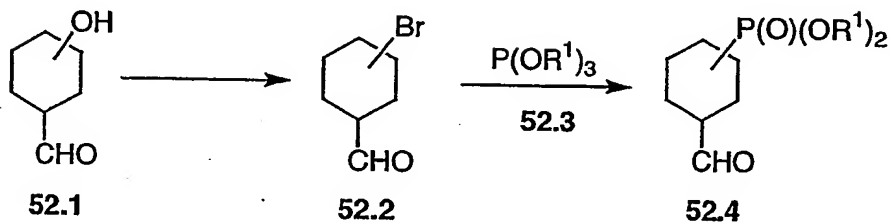


Example

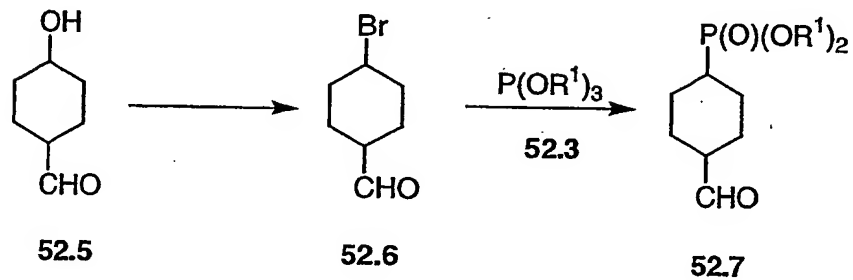


Scheme 52

Method

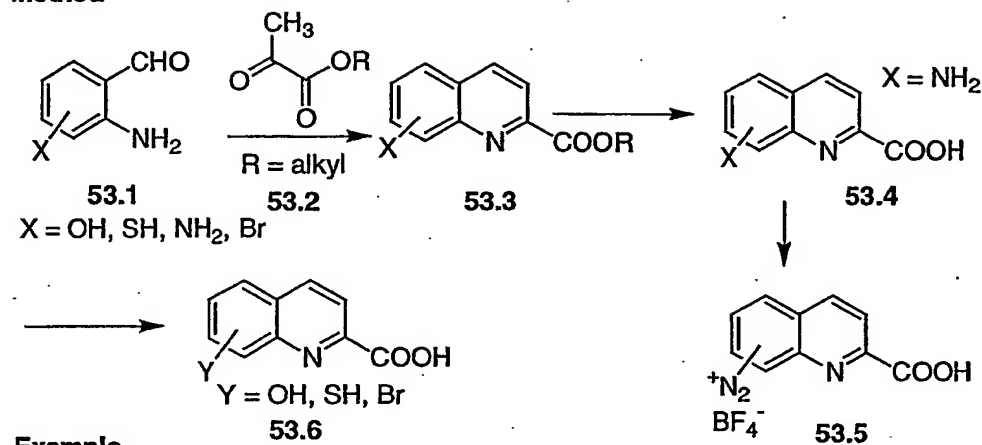


Example

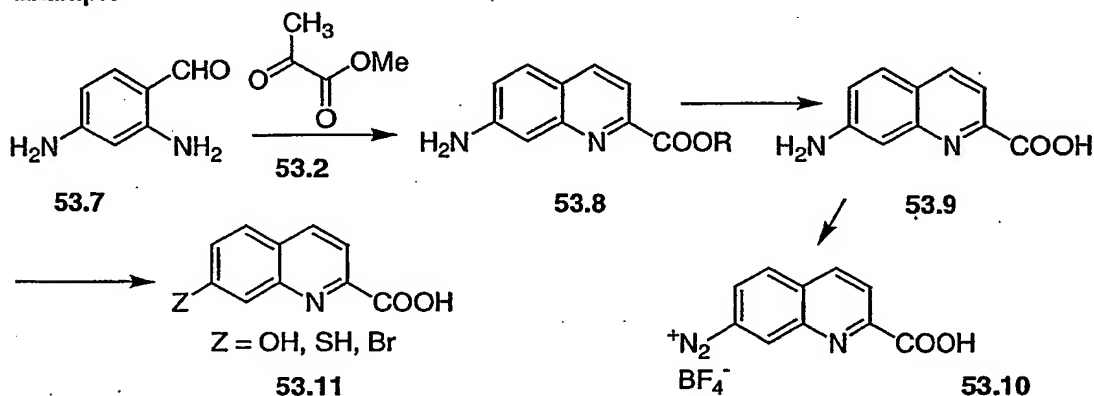


Scheme 53

Method



Example



Scheme 54 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester 54.1 is transformed, via a diazotization procedure as described above (Scheme 53) into the corresponding phenol or thiol 54.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 54.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 54.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the thioether products 54.5. Basic

hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 54.6.

For example, methyl 6-amino-2-quinoline carboxylate 54.7, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above,
5 into methyl 6-mercaptoquinoline-2-carboxylate 54.8. This material is reacted with a dialkyl hydroxymethylphosphonate 54.9 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 54.10. Basic hydrolysis then afford the carboxylic acid 54.11.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline
10 carboxylate 54.7, different aminoquinoline carboxylic esters 54.1, and/or different dialkyl hydroxymethylphosphonates 54.3 the corresponding phosphonate ester products 54.6 are obtained.

Scheme 55 illustrates the preparation of quinoline-2-carboxylic acids incorporating
15 phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 55.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 55.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001,
20 p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound 55.1 and the olefin 55.2 affords the olefinic
25 ester 55.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 55.4. Optionally, the unsaturated carboxylic acid 55.4 can be reduced to afford the saturated analog 55.5. The reduction reaction can be effected chemically, for example by the use of diimide, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5.
30 For example, methyl 7-bromoquinoline-2-carboxylate, 55.6, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate 55.7 (Aldrich) in the presence of 2 mol% of

tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 55.8. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 55.9. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product 55.10.

Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate 55.6, different bromoquinoline carboxylic esters 55.1, and/or different dialkyl alkenylphosphonates 55.2, the corresponding phosphonate ester products 55.4 and 55.5 are obtained.

Scheme 56 depicts the preparation of quinoline-2-carboxylic acids 56.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 56.1 is reacted with a phosphonate aldehyde 56.2 under reductive amination conditions, to afford the aminoalkyl product 56.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 56.4 is then hydrolyzed to yield the free carboxylic acid 56.5.

For example, methyl 7-aminoquinoline-2-carboxylate 56.6, prepared as described in J. Amer. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate 56.7 (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product 56.8. The ester is then hydrolyzed, as described above, to yield the carboxylic acid 56.9. Using the above procedures, but employing, in place of the formylmethyl phosphonate 56.2, different formylalkyl phosphonates, and/or different aminoquinolines 56.1, the corresponding products 56.5 are obtained.

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 56 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may be the same or different. The R¹ groups attached to a phosphonate esters 1-7, or to precursors thereto, may be changed using established chemical transformations. The interconversions
5 reactions of phosphonates are illustrated in Scheme 57. The group R in Scheme 57 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1-7 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1-7. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation
10 and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 57.1 into the corresponding phosphonate monoester 57.2 (Scheme 57, Reaction 1) can be accomplished by a number of methods. For example, the ester 57.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester
15 compound 57.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 57.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 57.2 can be effected by treatment of the ester 57.1 with a base such as aqueous
20 sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 57.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 57.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester
25 57.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 57.1 or a phosphonate monoester 57.2 into the
30 corresponding phosphonic acid 57.3 (Scheme 57, Reactions 2 and 3) can effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc.,

- Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 57.2 in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 57.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 57.2 in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 57.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.
- 10 Palladium catalyzed hydrogenolysis of phosphonate esters 57.1 in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters 57.1 in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

- The conversion of a phosphonate monoester 57.2 into a phosphonate diester 57.1 (Scheme 57, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate 57.2 is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yl-oxo)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester 57.2 to the diester 57.1 can be effected by the use of the Mitsunobu reaction, as described above (Scheme 54). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester 57.2 can be transformed into the phosphonate diester 57.1, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **57.2** is transformed into the chloro analog $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $\text{RP}(\text{O})(\text{OR}^1)\text{Cl}$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **57.1**.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ can be transformed into a phosphonate monoester $\text{RP}(\text{O})(\text{OR}^1)(\text{OH})$ (Scheme 57, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

A phosphonic acid $\text{R-link-P}(\text{O})(\text{OH})_2$ **57.3** can be transformed into a phosphonate diester $\text{R-link-P}(\text{O})(\text{OR}^1)_2$ **57.1** (Scheme 57, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.

Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **57.3** can be transformed into phosphonic esters **57.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **57.1**.

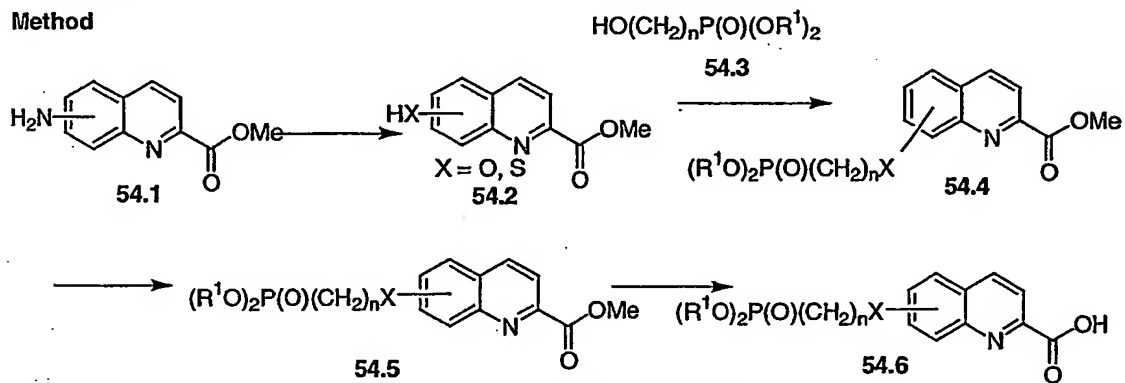
General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties (Schemes 21 - 56) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into carbinols (Schemes 21 - 26) are applicable to the introduction of phosphonate moieties into the oxirane, thiophenol, aldehyde and quinoline substrates, and the methods described herein for the introduction of phosphonate moieties into the oxirane,

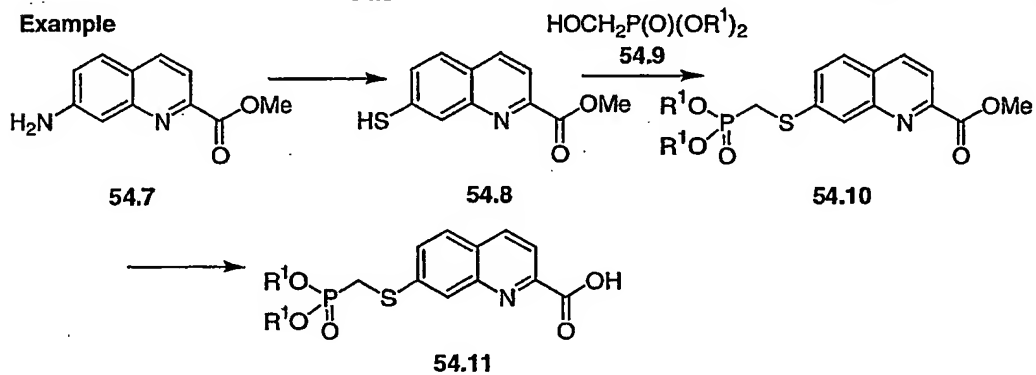
thiophenol, aldehyde and quinoline substrates, (Schemes 27 - 56) are applicable to the introduction of phosphonate moieties into carbinol substrates.

Scheme 54

Method

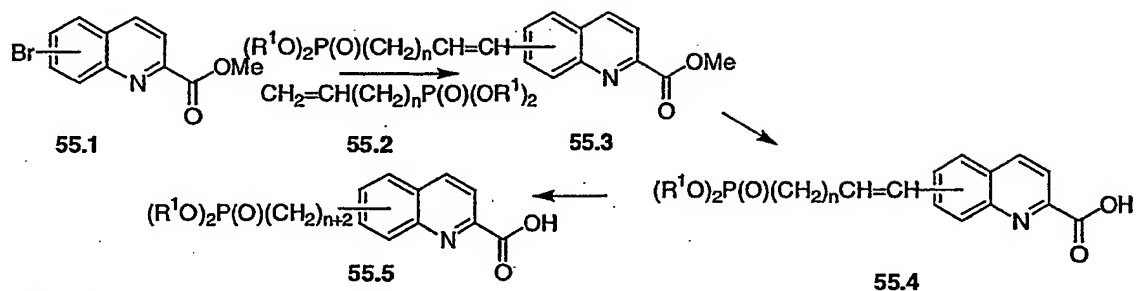


Example

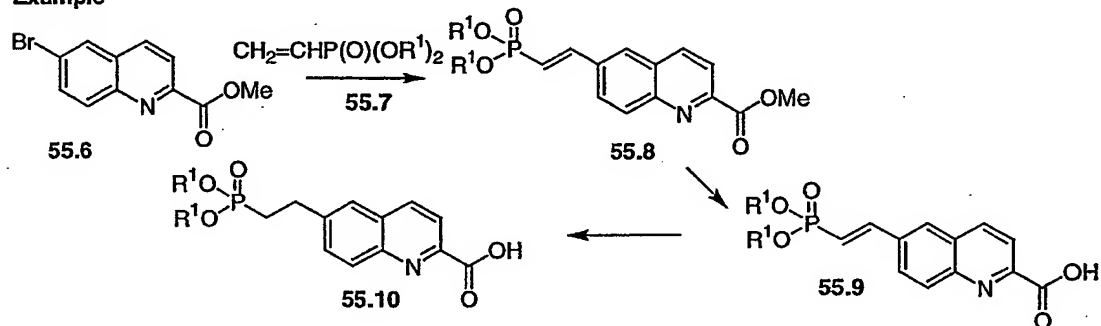


Scheme 55

Method

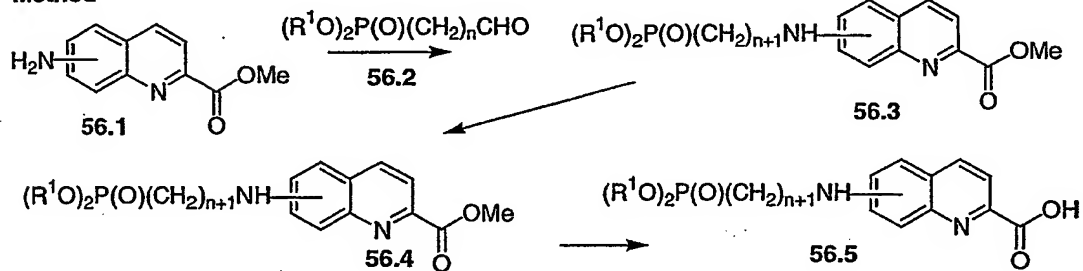


Example

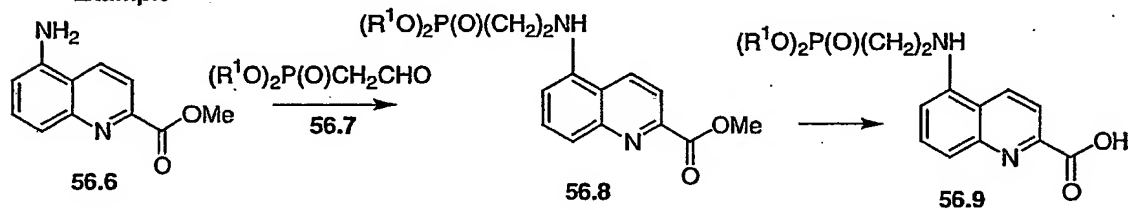


Scheme 56

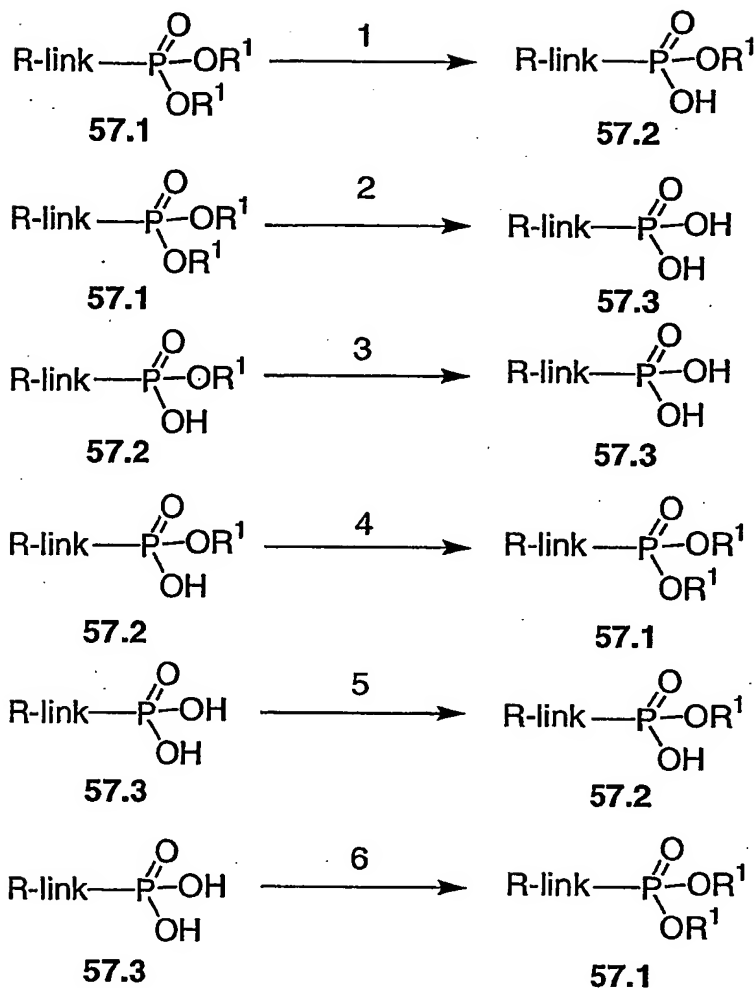
Method



Example



Scheme 57



Preparation of phosphonate intermediates 6 and 7 with phosphonate moieties incorporated into the group R^2COOH and R^5COOH .

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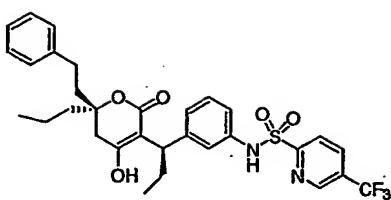
The chemical transformations described in Schemes 1 - 56 illustrate the preparation of compounds 1-5 in which the phosphonate ester moiety is attached to the carbinol moiety, (Schemes 21 - 26), the oxirane moiety (Schemes 27 - 29), the thiophenol moiety (Schemes 30 - 39), the aldehyde moiety (Schemes 40 - 52) or the quinoline moiety (Schemes 53 - 56). The various chemical methods employed for the preparation of phosphonate groups can, with appropriate modifications known to those skilled in the art, be applied to the introduction of phosphonate ester groups into the compounds R^2COOH and R^5COOH , as defined in Charts

10

2a, 2b and 2c. The resultant phosphonate-containing analogs, designated as $R^{2a}COOH$ and $R^{5a}COOH$ can then, using the procedures described above, be employed in the preparation of the compounds 6 and 7. The procedures required for the introduction of the phosphonate-containing analogs $R^{2a}COOH$ and $R^{5a}COOH$ are the same as those described above (Schemes 1, 5, 7 and 10) for the introduction of the R^2CO and R^5CO moieties.

Tipranavir-like phosphonate protease inhibitors (TLPPD)

Chart 1 illustrates the target compounds of the invention. A linkage group (link) is a portion of the structure that links two substructures, one of which is the scaffold having the structures shown above, the other a phosphonate moiety bearing the appropriate R and R^0 groups, as defined below. The link has at least one uninterrupted chain of atoms, other than hydrogen, typically ranging in up to 25 atoms, more preferably less than 10 atoms (hydrogen excluded). The link can be formed using a variety of functional groups such as heteroatom, carbon, alkenyl, aryl etc. Chart 2 illustrates the intermediate phosphonate compounds of this invention that are used in the preparation of the targets, Chart 1. Chart 3 shows some examples illustrated below of linking groups present in the structures in Chart 1 and 2. The R and R^0 groups can be both natural and un-natural amino acid esters linked through the amine nitrogen, or alternatively, one of the groups can be substituted for an oxygen linked aryl, alkyl, aralkyl group etc. Alternatively one of the groups may be an oxygen linked aryl, alkyl, aralkyl group etc and the other a lactate ester.



Tipranavir
US 5852195

Chart 1

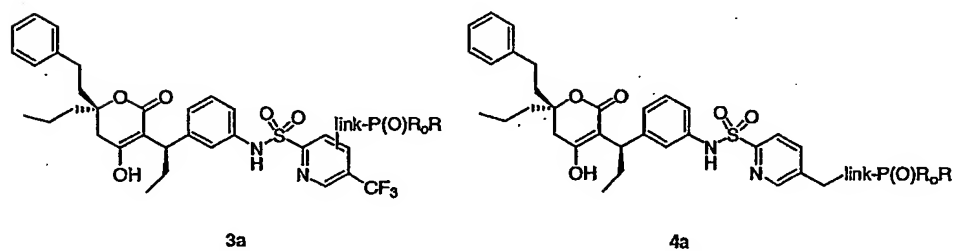
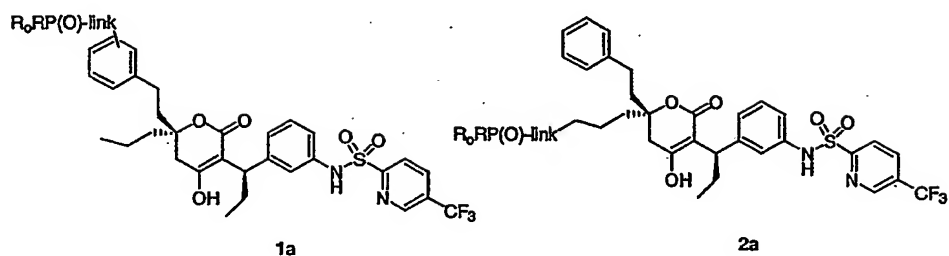
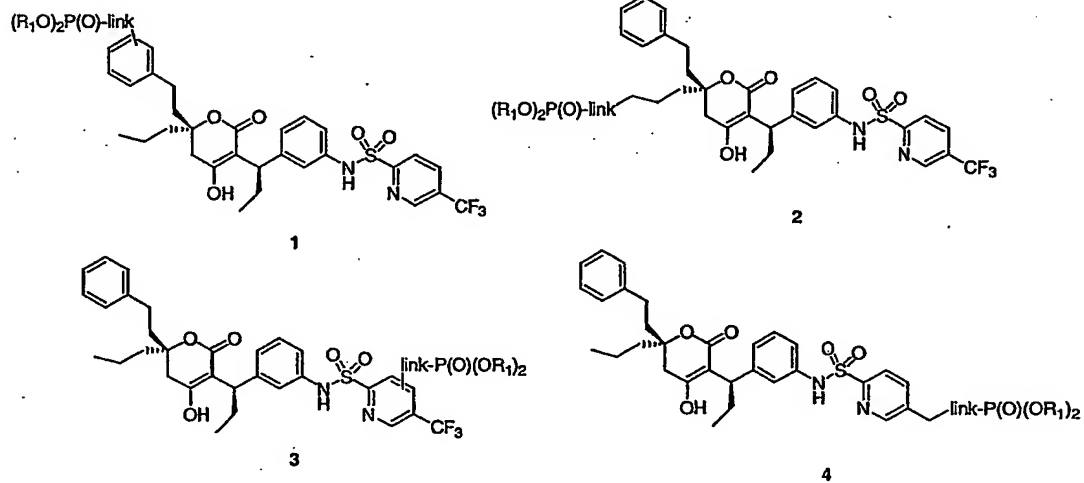
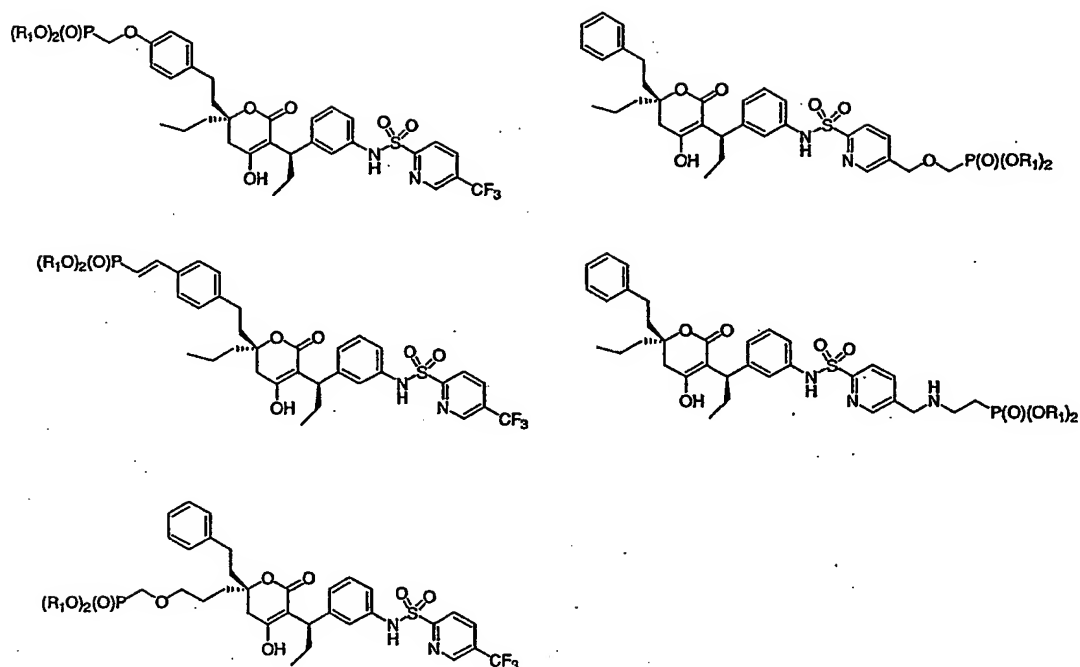


Chart 2



$R_1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

Chart 3



Phosphonate Interconversions

The final compounds described above are synthesized according to the methods described in the following Schemes 1-16. The intermediate phosphonate esters are shown in Chart 2 and these compounds can be used to prepare the final compounds illustrated above in Chart 1, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described in Scheme 16 below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link- $P(O)(OR^1)_2$, where R^1 is defined in Chart 2, or indeed the final stage of $P(O)RR^0$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the

substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-P(O)(OR¹)₂ or P(O)RR^o

In the succeeding examples, the nature of the phosphonate ester group P(O)(OR¹)₂ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 16). Examples shown in charts 1-3 indicate a specific stereochemistry. However, the methods are applicable to the synthesis all of the possible stereoisomers and the separation of possible isomers can be effected at any stage of the sequence after introduction of the stereocenter. The point in the synthetic sequence would be determined by the resolution that could be achieved in the separation by one skilled in the art.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of Intermediate Phosphonates shown in Chart 2

Scheme 1-3 illustrates the synthesis of target molecules of type 1, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The procedures described in J. Med. Chem. 1998, 41, p3467 are used to generate compounds of the type 1 from 1.2 in which A is Hydrogen. The conversion of 1.1 into 1.2 follows procedures described in Bioorg Med. Chem 1999, 7, p2775 for the preparation of a similar compound. The preparation of 1.1 is described in Scheme 13-14. For example, acid 1.1 is converted via the Weinreb amide to the ketone 1.2. The ketone 1.2 is then treated with 3-oxo-butyric acid methyl ester, as described in J. Med Chem. 1998, 41, 3467, to give the pyrone 1.3. A mixture of R and S isomers can be carried forward or alternatively separated by chiral chromatography at this stage. Aluminium chloride catalysed condensation of 3-nitrobenzaldehyde onto the pyrone 1.3, as described in J. Med

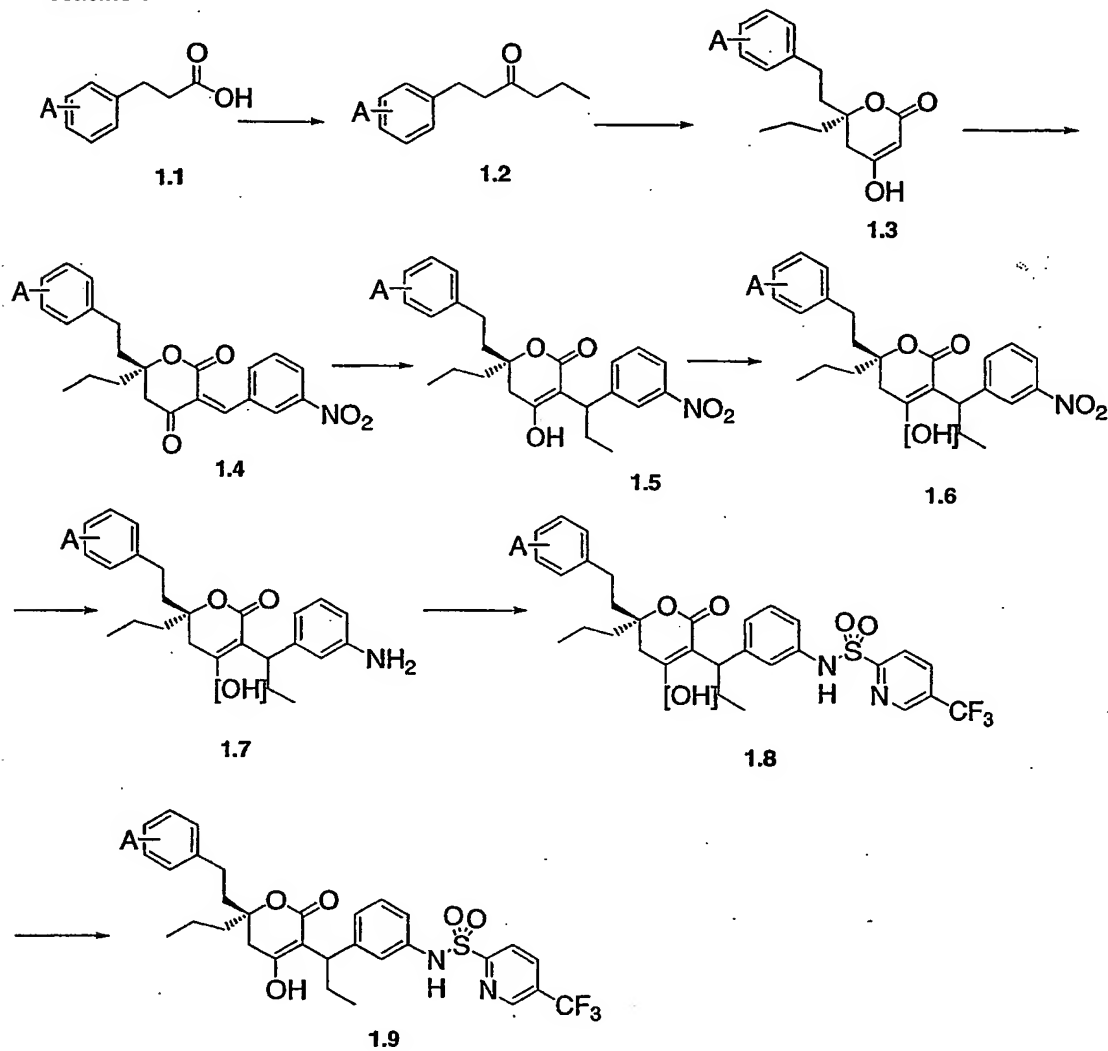
Chem. 1998, 41, 3467-3476, affords nitro pyrone **1.4**. Nitro pyrone **1.4** upon treatment with triethylaluminum in the presence of copper(1) bromide-dimethylsulfide as described in J. Med Chem. 1998, 41, 3467-3476 affords the dihydropyrone **1.5**. Protection of the dihydropyran hydroxyl in **1.5** with a suitable protecting group as described in Protective Groups in Organic
5 Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff gives the hydroxyl protected compound **1.6**. For example, treatment with SEMCl in the presence of base e.g. potassium carbonate, generates the SEM ether protected **1.6**. Catalytic hydrogenolysis of the nitro group, as described in J. Med Chem. 1998, 41, 3467-3476, affords the aryl amine **1.7** which is then coupled with the 5-trifluoromethyl-pyridine-2-sulfonyl
10 chloride in the presence of pyridine, as described in J. Med Chem. 1998, 41, 3467-3476 to afford the sulfonamide **1.8**. Finally, removal of the protecting group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff affords the product **1.9**. For example, treatment of the SEM protected product indicated above with TBAF produces the de-silylated (6R, 3R/S) product **1.9**. The
15 diastereoisomers are then separated through silica gel chromatography.

Scheme 2 also illustrates the synthesis of target molecules of type **1**, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂ but the products in this example have the absolute stereochemistry (6R, 3R). The ketone **1.2**, prepared in Scheme 1, is transformed
20 into the dihydropyrone **2.2** as described in Drugs of the Future, 1998, 23(2), p146. This 2 step reaction involves reaction of the ketone with dioxalone **2.1**, prepared as described in Drugs of the Future, 1998, 23(2), p146 in the presence of Ti(OBu)Cl₃, followed by treatment with a base such as potassium tert-butoxide. Treatment of the dihydropyrone **2.2** with the same procedures reported in Scheme 1 for the conversion of **1.5** into **1.9** then affords the final
25 product **1.9** in chiral form (6R, 3R). For example, the pyrone hydroxyl **2.2** is first protected as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.249ff, to afford **2.3** and then the dibenzyl groups are removed from **2.3** by catalytic hydrogenolysis as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.579 to afford the amine
30 product **1.7**. Amine **1.7** is then converted into **1.9** as described in Scheme 1.

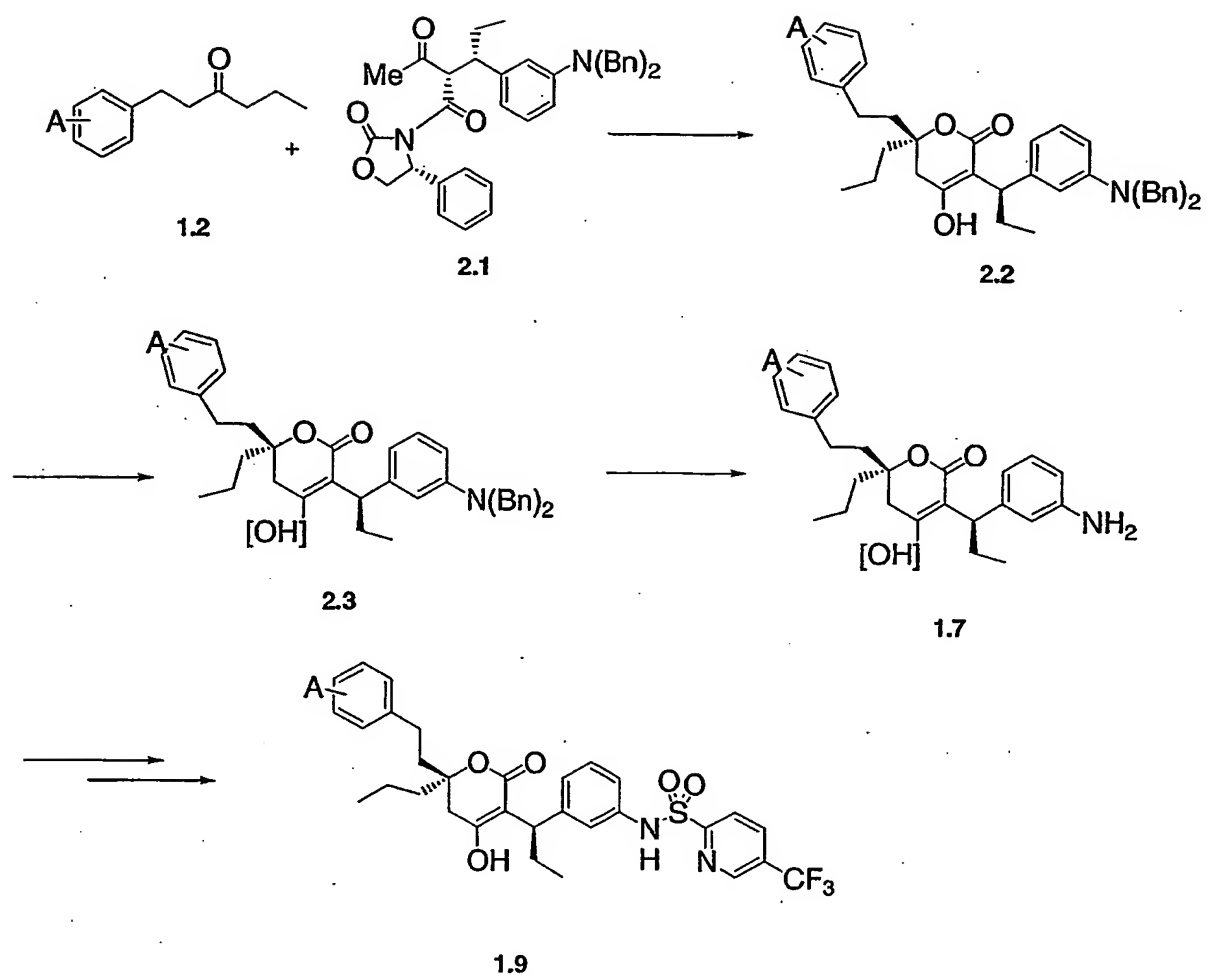
The reactions shown in Scheme 1-2 illustrate the preparation of the compounds 1.9 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 3 depicts the conversion of the compounds 1.9 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 1. In this procedure, the compounds 1.9 are

5 converted, using the procedures described below, Schemes 10-15, into the compounds 1.

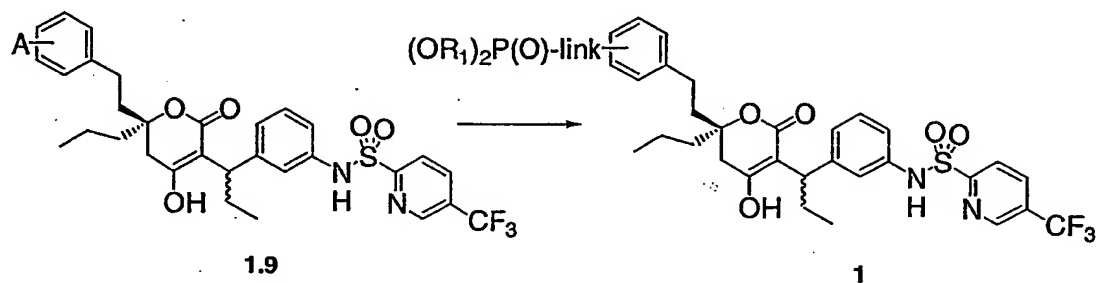
Scheme 1



Scheme 2



Scheme 3

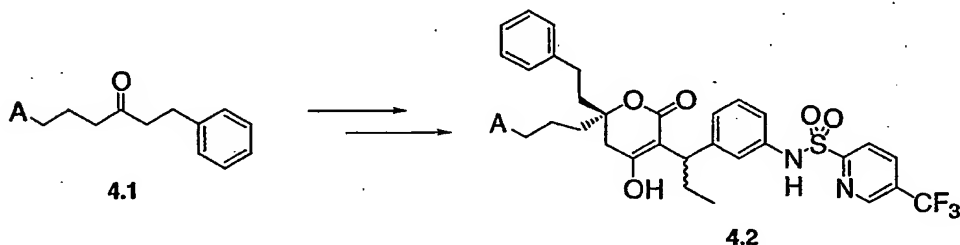


Scheme 4 illustrates the synthesis of target molecules of type 2, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The acid 4.1 prepared as described below (Scheme 15), is converted into 4.2 using the procedures described in Scheme 1 or Scheme 2.

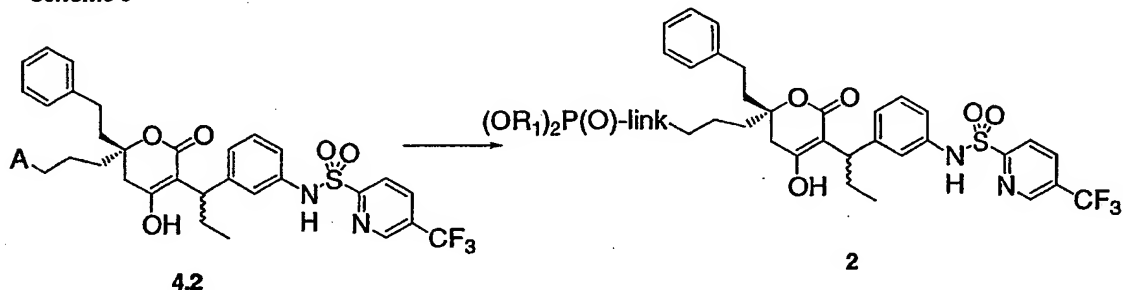
- 5 The reactions shown in Scheme 4 illustrate the preparation of the compounds 4.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 5 depicts the conversion of the compounds 4.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2. In this procedure, the compounds 4.2 are converted, using the procedures described below, Schemes 10-15, into the compounds 2.

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Scheme 4



Scheme 5

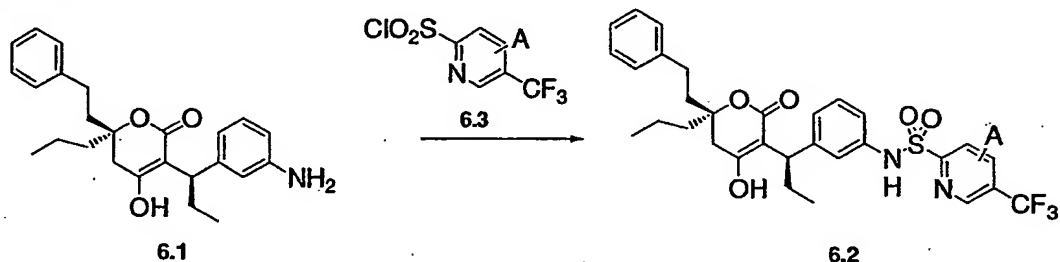


- 15 Scheme 6-7 illustrates the synthesis of target molecules of type 3, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The amine 6.1 prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide 6.2 using the procedures described in Scheme 1 or Scheme 2 for the preparation of 1.8 from 1.7. The synthesis of the sulfonyl chlorides 6.3 is shown below in Schemes 11-12.

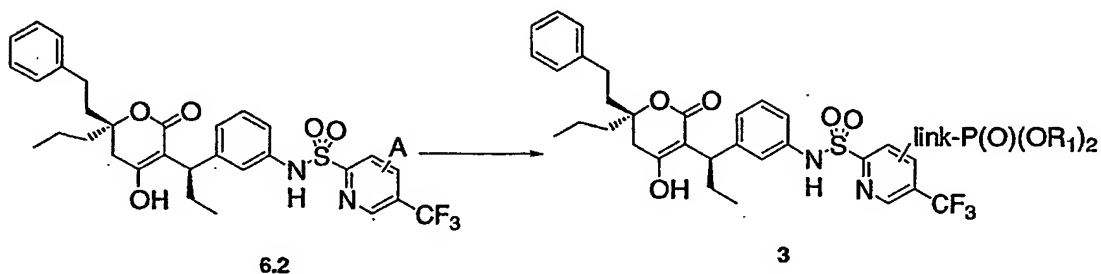
- 20 The reactions shown in Scheme 6 illustrate the preparation of the compounds 6.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 7 depicts the conversion of the compounds 6.2 in which A is [OH], [SH], [NH],

Br etc, into the phosphonate esters 3. In this procedure, the compounds 6.2 are converted, using the procedures described below, Schemes 10-15, into the compounds 3.

Scheme 6



Scheme 7



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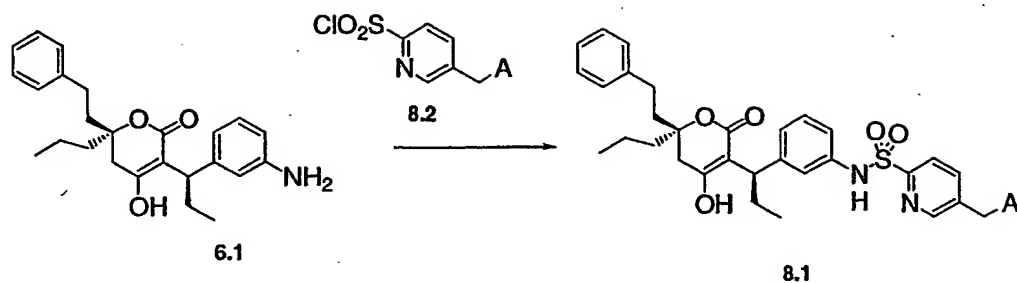
Scheme 8 illustrates the synthesis of target molecules of type 4, chart 2, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR¹)₂. The amine 6.1 prepared as described in Drugs of the Future, 1998, 23(2), p146 or US 5852195, is converted into the sulfonamide 8.1 by treatment with 8.2 using the procedures described in Scheme 1 or Scheme 2. The synthesis of the sulfonyl chlorides 8.2 is shown below in Scheme 10.

10

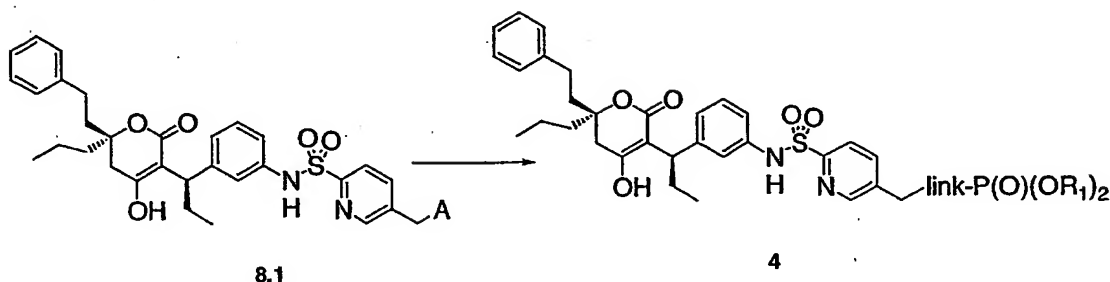
The reactions shown in Scheme 8 illustrate the preparation of the compounds 8.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 9 depicts the conversion of the compounds 8.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4. In this procedure, the compounds 8.1 are converted, using the procedures described below, Schemes 10-15, into the compounds 4.

15

Scheme 8



Scheme 9



Preparation of phosphonate reagents used in the synthesis of compounds 1-4

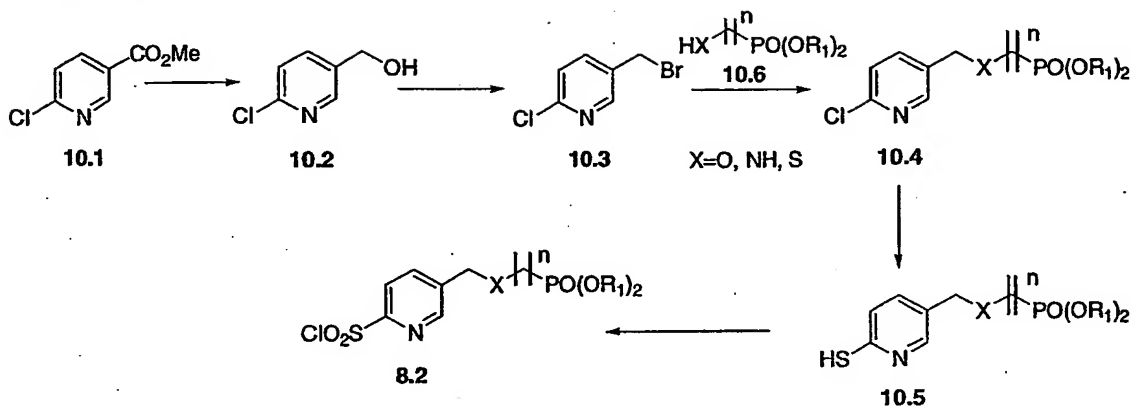
- 5 Schemes 10 describes the preparation of phosphonate-containing derivatives 8.2, in which the phosphonate is linked through a heteroatom, which are employed in the preparation of the phosphonate ester intermediates 4. The pyridyl ester 10.1 (Acros) is first reduced to the alcohol 10.2. This transformation involves reducing the ester with lithium aluminium hydride, or other reducing agent, in an inert solvent such as THF or dioxane. Alcohol 10.2 is then
- 10 converted to the bromide 10.3 through typical hydroxyl to bromide conversion conditions described in Comprehensive Organic Transformations, R.C. Larock, 2nd edition, p693-697. For instance, treatment of 10.2 with carbon tetrabromide and triphenylphosphine in THF or dioxane affords the bromide 10.3. Treatment of the bromide 10.3 with a thiol, amino, or hydroxyl alkyl phosphonate 10.6 then affords the phosphonate product 10.4. The reaction is
- 15 performed in the presence of a base, in a polar aprotic solvent such as dioxane or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 10.6. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. The chloride 10.4 is then treated KHS in
- 20 methanol, as described in Justus Liebigs Annalen Chemie, 1931, p105 or thiourea followed by

potassium hydroxide treatment, as described in Heterocycles 1984, p117, to give the α -sulfide 10.5. If appropriate, reactive groups e.g. amines in the phosphonate chain, are protected using methods known to one skilled in the art. The α -sulfide 10.5 is then converted to the sulfonyl chloride 8.2 by treatment with chlorine in HCl, as described in Synthesis 1987, 4, p409, or J. Med. Chem 1980,12, p1376.

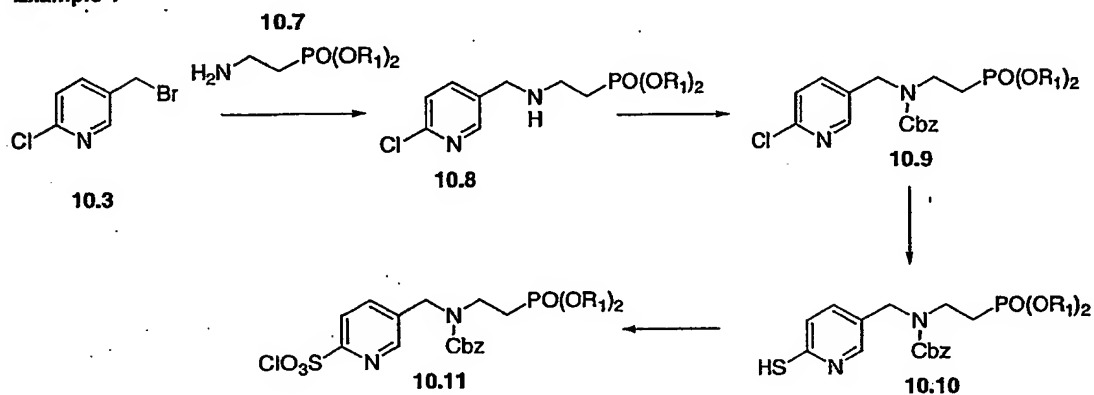
For example, the pyridyl bromide 10.3, described above, is treated with amino phosphonate 10.7, prepared as described in J. Org. Chem. 2000, 65, p676, in the presence of potassium carbonate and DMF to afford the phosphonate product 10.8. Protection of the amine by conversion to the CBZ carbamate 10.9 is performed by treatment of 10.8 with benzyl chloroformate in the presence of triethylamine. Further treatment of 10.9 with thiourea in ethanol at reflux followed by treatment with potassium hydroxide in water then affords the thiol 10.10. Thiol 10.10 is then treated with chlorine in HCl (aqueous) to afford the sulfonyl chloride 10.11. Using the above procedures, but employing, in place of the amino alkyl phosphonate 10.7, different alkyl phosphonates 10.6, the corresponding products 8.2 are obtained.

Alternatively (Example 2), illustrates the preparation of phosphonates in which the link is through an oxygen atom. The pyridyl bromide 10.3 described above, is treated with hydroxyl phosphonate 10.12, prepared as described in Synthesis 1998, 4, p327, in the presence of potassium carbonate and DMF to afford the phosphonate product 10.13. Further treatment of 10.13, as described above, for the conversion of 10.8 into 10.11 affords the sulfonyl chloride 10.16. Using the above procedures, but employing, in place of the hydroxy alkyl phosphonate 10.12, different alkyl phosphonates 10.6 the corresponding products 8.2 are obtained.

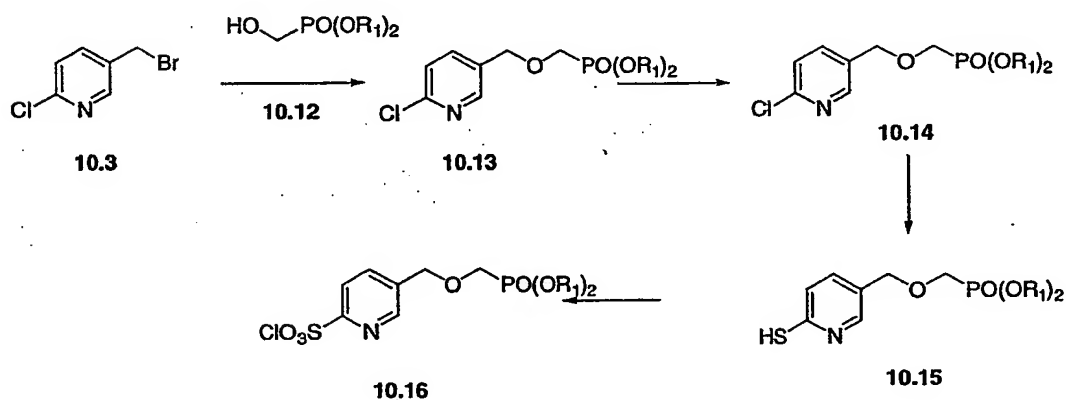
Scheme 10



Example 1



Example 2



- 5 Schemes 11-12 describe the preparation of phosphonate-containing derivatives 6.3, which are employed in the preparation of the phosphonate ester intermediates 3. Scheme 11 illustrates compounds of type 6.3 in which the link is through a oxygen, sulfur or nitrogen heteroatom.

Pyridyl halide 11.1 is treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate 10.6 to give the product 11.3. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant 10.6. For example, if X is O, a strong
5 base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Upon formation of 11.3 the pyridine is converted to the α -chloro pyridine 11.4 by treatment with chlorine at high temperature in a sealed vessel as described in Recl. Trav. Chim Pays-Bas 1939, 58, p709 or, preferably, the α -chloro compound is generated by treatment of
10 11.3 with butyl lithium in hexane and $\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$ followed by addition of a chloride source such as hexachloroethane, as described in Chem Commun. 2000, 11, p951. Chloride 11.4 is then converted to the thiol 11.4 as described above (Scheme 10). Thiol 11.5 is then converted to the sulfonyl chloride 6.3 as described in Scheme 10.

15 For example, bromo pyridine (Apollo) 11.6 is treated with amine 10.7 in the presence of cesium carbonate in THF or alternative solvent at reflux to give the amine 11.7. The amine is then converted to the sulfonyl chloride 11.9 through the intermediate chloride 11.8 as described in Scheme 10. Using the above procedures, but employing, in place of the amino alkyl phosphonate 10.7, different alkyl phosphonates 10.6, and in place of the pyridine 11.6
20 different halo pyridines 11.1, the corresponding products 6.3 are obtained.

Alternatively the bromo pyridine 11.6 (Apollo) is treated with thiol 11.10, prepared as described in Zh. Obschei. Khim 1973, 43, p2364, in the presence of cesium carbonate in THF or alternative solvent at reflux to give the thiol 11.11. The thiol is then converted to the
25 sulfonyl chloride 11.12 as described above for the conversion of 11.7 into 11.9. Using the above procedures, but employing, in place of the thiol alkyl phosphonate 11.10, different alkyl phosphonates 10.6, and in place of the pyridine 11.6 different halo pyridines 11.1, the corresponding products 6.3 are obtained.

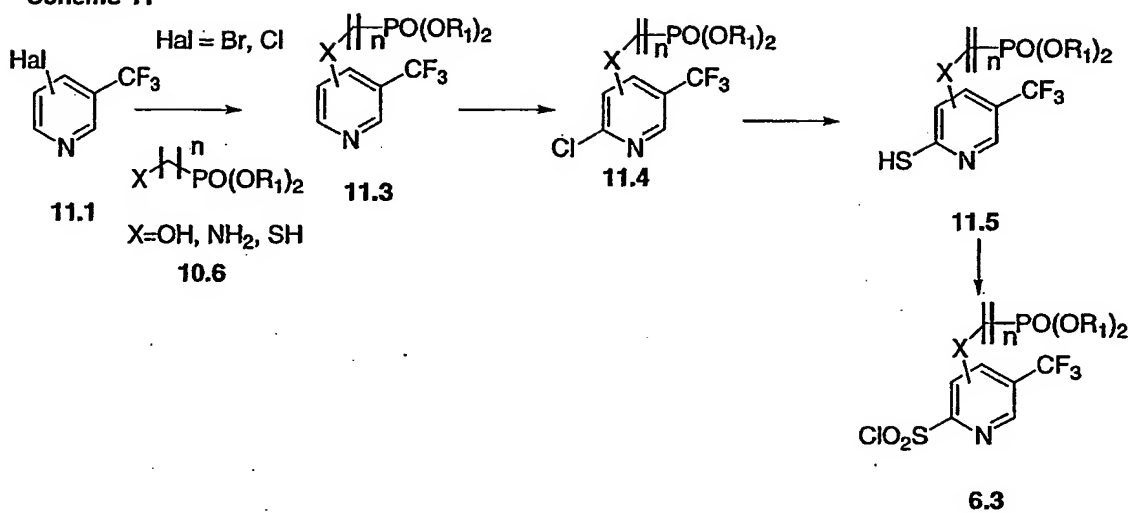
30 Scheme 12 illustrates compounds of type 6.3 in which the phosphonate is attached through an unsaturated or saturated carbon linker. In this procedure, pyridyl bromo compound 11.1 is treated under a palladium catalyzed Heck coupling conditions with the alkene 12.1 to give the

coupled alkene 12.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of
5 a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 12.2. Optionally, the product 12.2 can be reduced to afford the saturated phosphonate 12.4. Methods for the reduction of carbon-carbon double bonds are described, for example, in *Comprehensive*
10 *Organic Transformations*, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide. Following the Heck reaction or reduction the pyridyl compounds 12.2 and 12.4 are converted to the sulfonyl chlorides 12.3 and 12.5 respectively, using the same procedures described in Scheme 11 for the conversion of 11.3 into 6.3

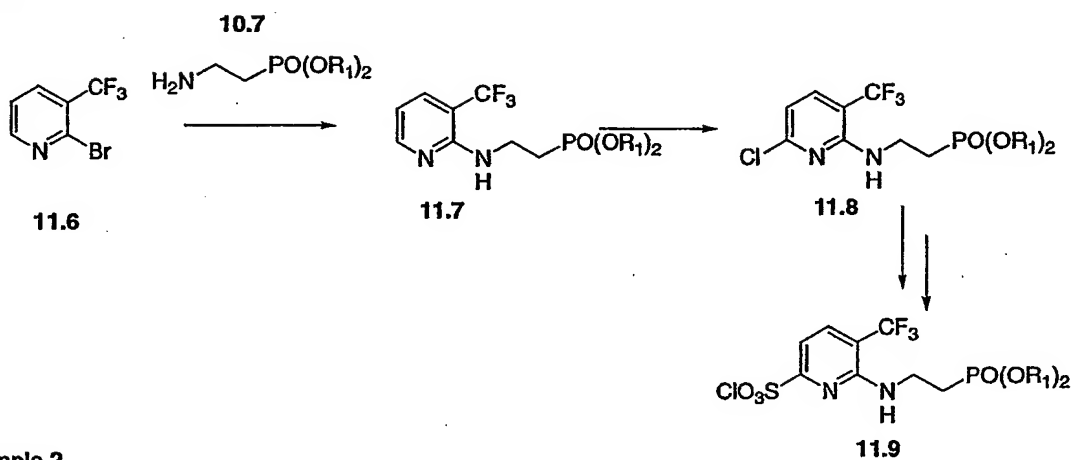
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For example, pyridine 11.6 (Aldrich) is reacted with a dialkyl propenyl phosphonate 12.6, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, in the presence of bis(triphenylphosphine) palladium(II) chloride, as described in *J. Med. Chem.*, 1992, 35, 1371, to afford the coupled product 12.7. The product 12.7 is then reduced, for example by
20 reaction with diimide, as described in *J. Org. Chem.*, 30, 3965, 1965, to afford the saturated product 12.9. Conversion of the products 12.7 and 12.9 into the sulfonyl chlorides 12.8 and 12.10 respectively follows the same procedures described above for the conversion of pyridine 11.7 into 11.9. Using the above procedures, but employing, in place of the halo pyridine compound 11.6, different pyridines 11.1, and/or different phosphonates 12.1 in place of 12.6,
25 the corresponding products 12.3 and 12.5 are obtained.

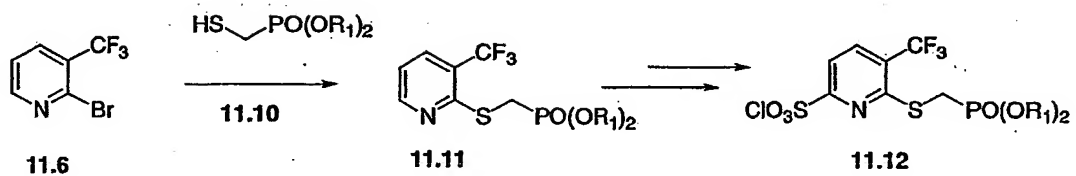
Scheme 11



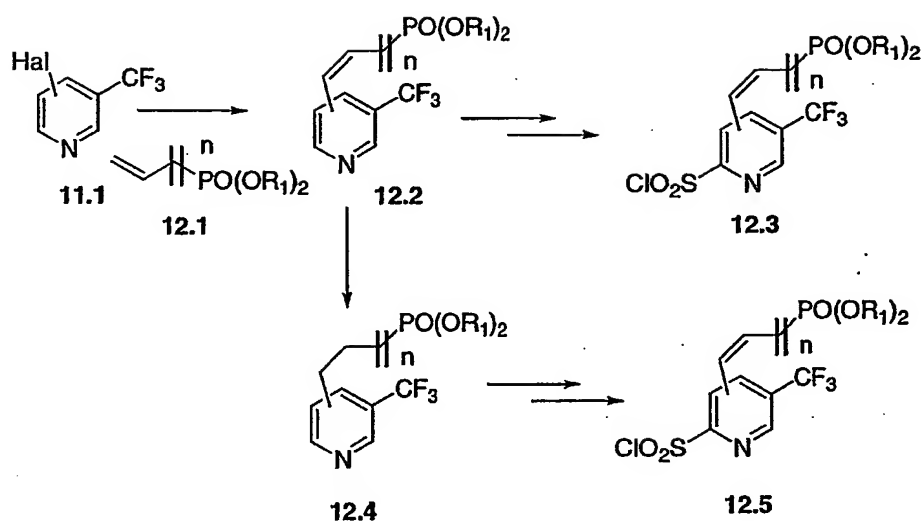
Example 1



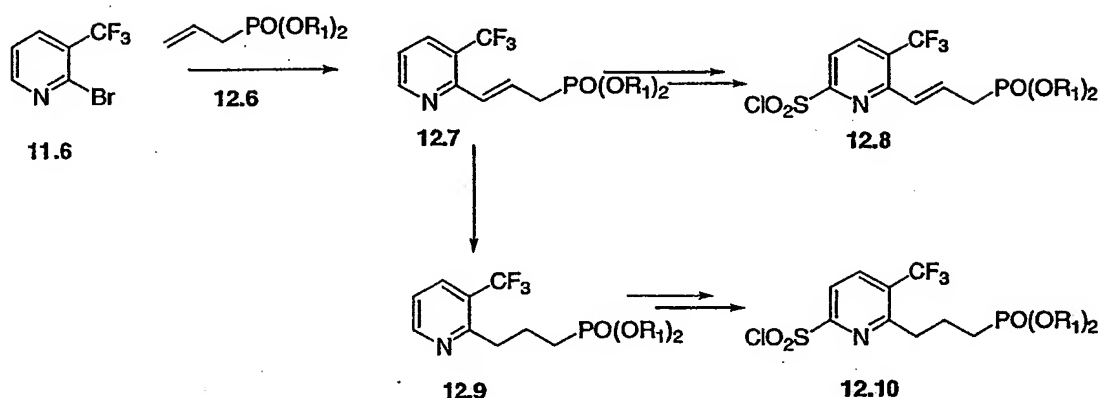
Example 2



Scheme 12



Example 1



- 5 Schemes 13-14 illustrate the preparation of phosphonate containing compounds 1.1 that are used in the preparation of the compounds of type 1, chart 2. Scheme 13 illustrates the preparation of phosphonates 1.1 in which the phosphonate is attached through a heteroatom such as S, O or N. The aryl halide 13.1 bearing a hydroxyl, amino or thiol group, is treated with one equivalent of the phosphonate alkylating agent 13.2, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl etc, in the presence of base e.g. potassium or cesium carbonate in DMF, to give the compound 13.3. The product 13.3 is then converted to the alkene 13.4 using a palladium mediated Heck coupling with Methyl acrylate as described
- 10

above, Scheme 12. The acrylate is reduced as described in Scheme 12 and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

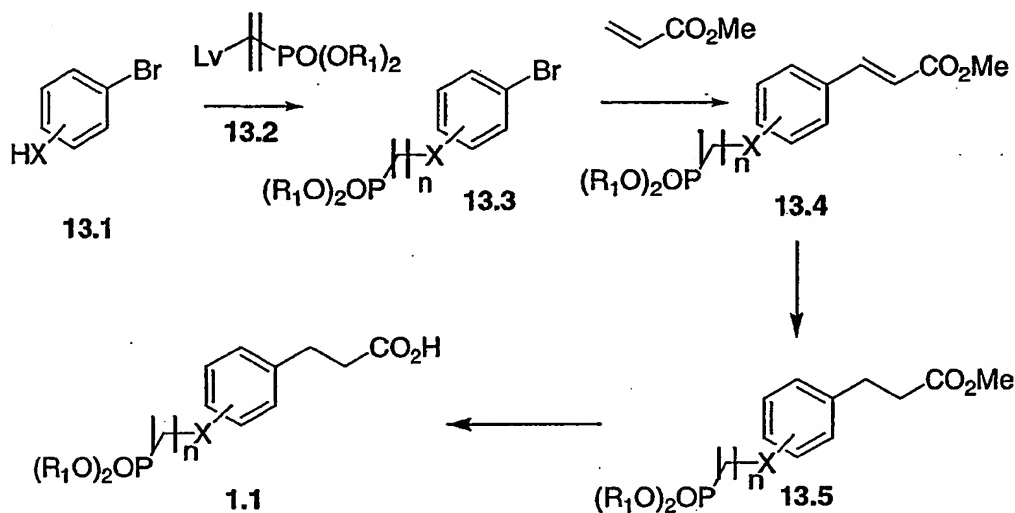
For example, the halide 13.6 (Aldrich) is treated with triflate phosphonate 13.7, prepared as described in Tet. Lett. 1986, 27, p1497, and potassium carbonate in DMF, to give the ether 13.8. The ether is then treated with methyl acrylate under Heck coupling conditions as described in J. Med. Chem. 1992, 35, p1371, to give the alkene 13.9. 13.9 is reduced by treatment with diimide, as described analogously in Bioorg Med. Chem. 1999, 7, p2775 to give the saturated aryl ester 13.10. Treatment of 13.10 with lithium hydroxide in THF and water then affords the acid 13.11. Using the above procedures, but employing, in place of the aryl halide 13.6, different aryl halides 13.1, and/or different phosphonates 13.2 in place of 13.7, the corresponding products 1.1 are obtained.

Scheme 14 illustrates the preparation of phosphonates 1.1 in which the link is through a carbon bond and a nitrogen heteroatom. The aryl halide bearing an carbonyl group is treated with one equivalent of the amino alkyl phosphonate 14.2 under reductive amination conditions to give the amine 14.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 14.3. The amine product 14.3 is then converted to the alkene 14.4 using a palladium mediated Heck coupling with Methyl acrylate as described above, Scheme 13. The acrylate is then reduced as described in Scheme 13 to give 14.5, and then the ester is hydrolyzed by treatment with base such as lithium or sodium hydroxide to afford the acid 1.1.

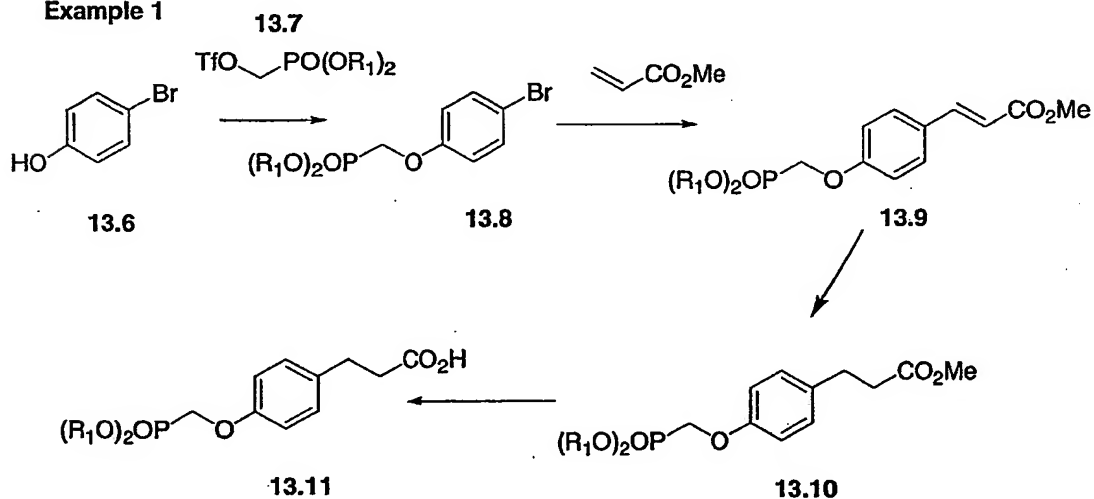
For example, the halide 14.6 (Aldrich) is treated with amino phosphonate 10.7, prepared as described above, in methanol for 30 min. After 30 min sodium borohydride is added to give the amine 14.7. The amine 14.7 is then treated with methyl acrylate under Heck coupling conditions as described above, to give the alkene 14.8. Alkene 14.8 is reduced as described in Scheme 13 to give the saturated ester 14.9. Treatment of 14.9 with lithium hydroxide in THF and water then affords the acid 14.10. Using the above procedures, but employing, in place of

the aryl halide 14.6, different aryl halides 14.1, and/or different amino phosphonates 14.2 in place of 10.7, the corresponding products 1.1 are obtained.

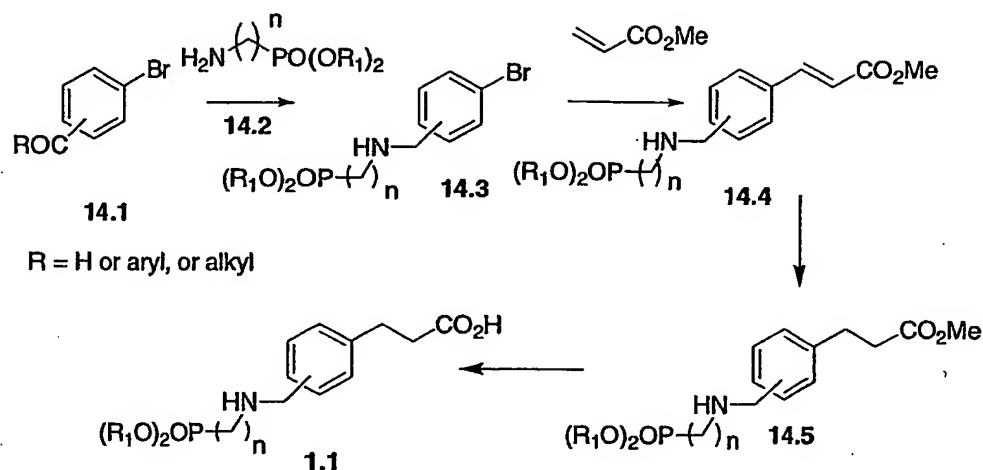
Scheme 13



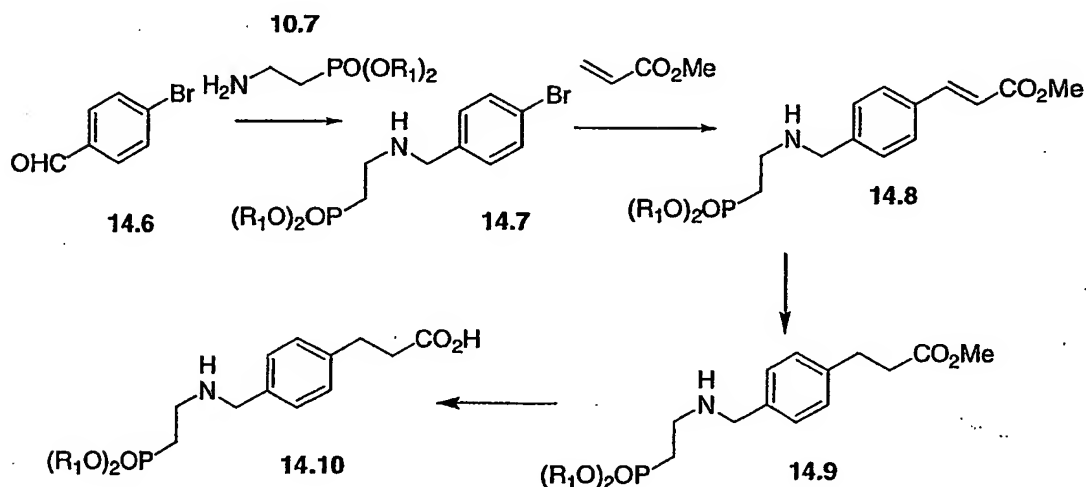
Example 1



Scheme 14



Example 1

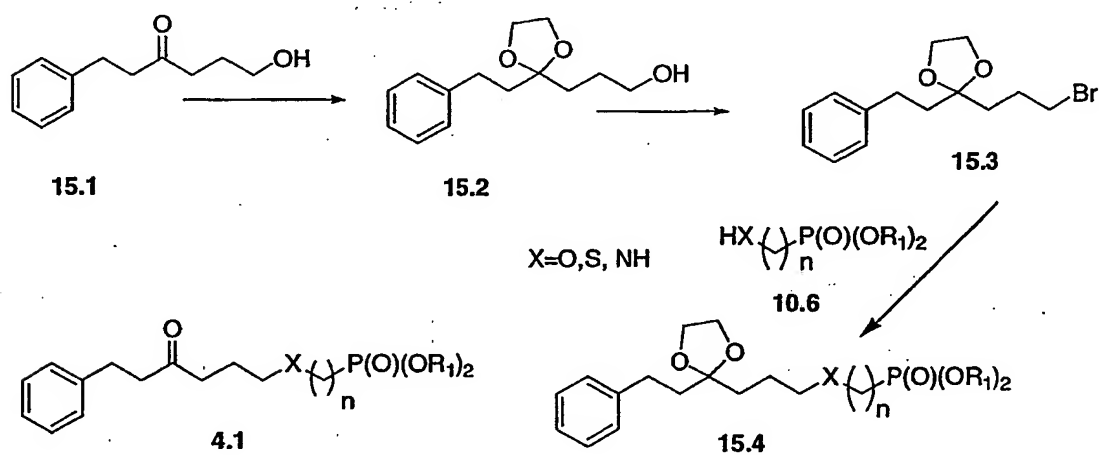


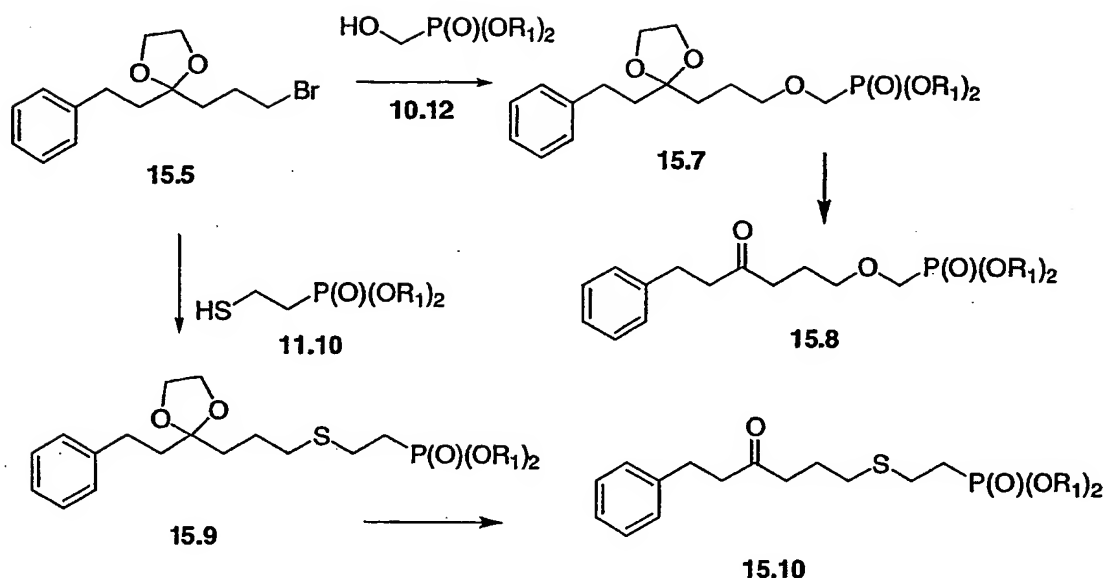
- 5 Scheme 15 describes the preparation of phosphonate-containing derivatives 4.1 which are employed in the preparation of the phosphonate ester intermediates 2, chart 2. The alcohol 15.1 prepared as described in J. Org Chem. 1994, 59, p3445, is treated with ethylene glycol and a catalytic amount of tosic acid in benzene at reflux to give the 1,3-dioxalane 15.2. The dioxalane is then treated with carbon tetrabromide and triphenyl phosphine in acetonitrile, or
- 10 alternate conditions as described in Comprehensive Organic Transformations, R.C. Larock, 2nd editions, p693-697, to generate the bromide 15.3. Bromide 15.3 is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate 10.6 to give the product 15.4. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan

or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **10.6**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Following preparation of **15.4** the dioxalone is removed as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p.317.

For example, **15.5** described above, is treated with alcohol **10.12**, prepared as described in Scheme **10**, in DMF and potassium carbonate at ca 80 °C to give the phosphonate **15.7**. Alternatively bromide **15.5** is then heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphosphonate **11.10**, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990, in the presence of sodium carbonate, to afford the thioether product **15.9**. Treatment of **15.7** and **15.9** with aqueous HCl in THF then affords the ketones **15.8** and **15.10** respectively. Using the above procedures, but employing, in place of **10.12** and **11.10**, different alkyl phosphonates **10.6** the corresponding products, **4.1** are obtained.

Scheme 15



Example 1**General applicability of methods for introduction of phosphonate substituents.**

The procedures described for the introduction of phosphonate moieties (Schemes 10-15) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, for example, the methods described above for the introduction of phosphonate groups onto the pyridyl ring of 11.1, are also applicable to the introduction of phosphonate moieties onto the aryl rings of 13.1 and 14.1, and the reverse is also true.

10 Interconversions of the phosphonates between R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

The schemes above describe the preparation of phosphonates of general structure R-link-P(O)(OR¹)₂ in which the R¹ groups are defined as indicated in Chart 2, and the R group refers to the scaffold. The R¹ groups attached to the phosphonate esters in Chart 2 may be changed using established chemical transformations. The interconversion reactions of the phosphonates attached through the link group to the scaffold (R) are illustrated in Scheme 16. The interconversions may be carried out in the precursor compounds or the final products using the methods described below. The methods employed for a given phosphonate

transformation depend on the nature of the substituent R^1 . The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maier, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 16.1 into the corresponding phosphonate monoester 16.2 (Scheme 16, Reaction 1) can be accomplished by a number of methods. For example, the ester 16.1 in which R^1 is an aralkyl group such as benzyl, can be converted into the monoester compound 16.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 16.1 in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 16.2 can be effected by treatment of the ester 16.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

Phosphonate diesters 16.2 in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 16.2 in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, can be converted into the monoester 16.2 in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38 3224 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester 16.1 or a phosphonate monoester 16.2 into the corresponding phosphonic acid 16.3 (Scheme 16, Reactions 2 and 3) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester 16.2 in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid 16.3 by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester 16.2 in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid 16.3 by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous

ethanol, for example using the procedure described in *Helv. Chim. Acta.*, 68, 618, 1985.

Palladium catalyzed hydrogenolysis of phosphonate esters **16.1** in which R^1 is benzyl is described in *J. Org. Chem.*, 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **16.1** in which R^1 is phenyl is described in *J. Amer. Chem. Soc.*, 78, 2336, 1956.

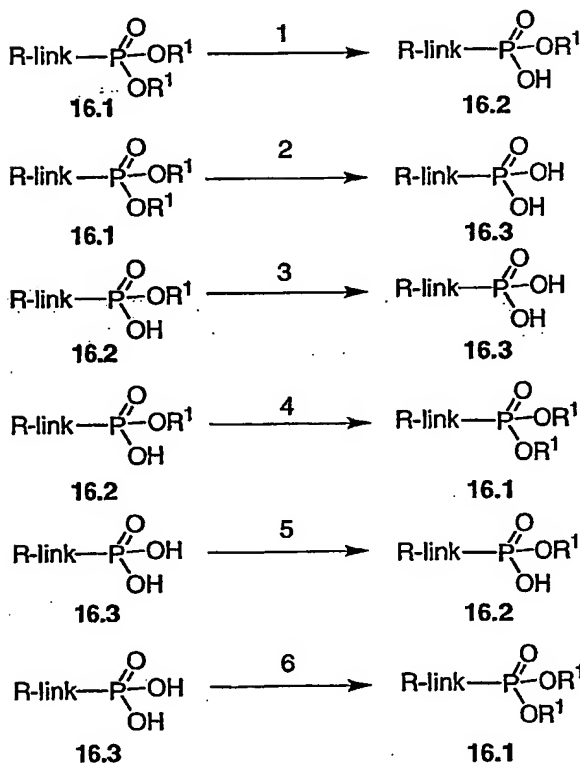
- 5 The conversion of a phosphonate monoester **16.2** into a phosphonate diester **16.1** (Scheme 16, Reaction 4) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **16.2** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a
- 10 carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the
- 15 reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine.. Alternatively, the conversion of the phosphonate monoester **16.1** to the diester **16.1** can be effected by the use of the Mitsunobu reaction. The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **16.2**
- 20 can be transformed into the phosphonate diester **16.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the phosphonate diester in a
- 25 two step procedure. In the first step, the phosphonate monoester **16.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in *Organic Phosphorus Compounds*, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate
- 30 diester **16.1**.

A phosphonic acid R-link-P(O)(OH)₂ can be transformed into a phosphonate monoester RP(O)(OR¹)(OH) (Scheme 16, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester R-link-P(O)(OR¹)₂ 16.1, except that only one molar proportion of the component R¹OH or R¹Br is employed. A phosphonic acid R-link-

- 5 P(O)(OH)₂ 16.3 can be transformed into a phosphonate diester R-link-P(O)(OR¹)₂ 16.1 (Scheme 16, Reaction 6) by a coupling reaction with the hydroxy compound R¹OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70°. Alternatively, phosphonic acids 16.3 can be transformed into phosphonic esters 16.1 in which R¹ is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R¹Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester 16.1.

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Scheme 16



Amprenavir-like phosphonate protease inhibitors (AMLPPI)**5 Preparation of the intermediate phosphonate esters 1-13.**

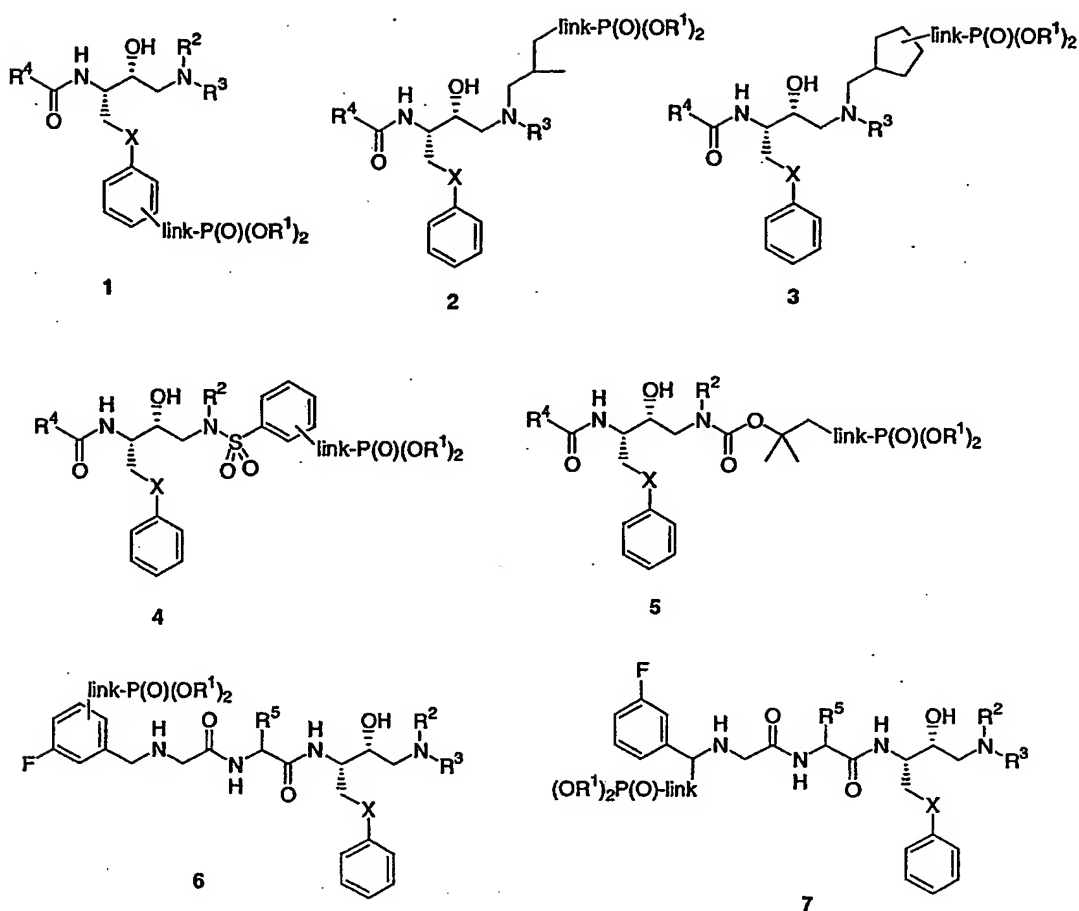
The structures of the intermediate phosphonate esters 1 to 13 and the structures of the component groups R^1 , R^5 , X of this invention are shown in Charts 1 - 2. The structures of the R^2NH_2 components are shown in Chart 3; the structures of the R^3-Cl components are shown
10 in Chart 4; the structures of the R_4COOH groups are shown in Chart 5a-c; and the structures of the $R^9CH_2NH_2$ amine components are illustrated in Chart 6.

Specific stereoisomers of some of the structures are shown in Charts 1 - 6; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 13. Subsequent chemical modifications to the compounds 1 to 10, as described herein, permit the synthesis of the final
15 compounds of this invention.

The intermediate compounds 1 to 10 incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 7, and 8 illustrate examples of the linking groups present in the structures 1 - 10.

20 Schemes 1 - 99 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1 - 10, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 11, 12 and 13, in which a phosphonate moiety is incorporated into one of the groups R^4 , R^3 , R^2 , respectively, is also described below.

Chart 1

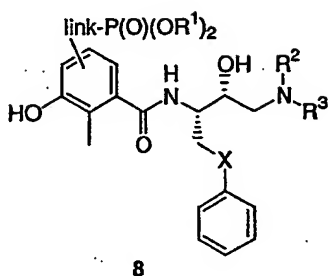


$R^1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$

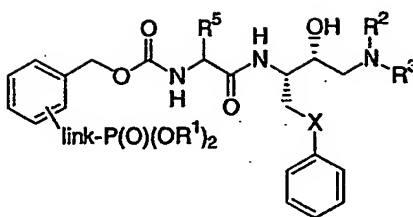
$X = \text{S or direct bond}$

$R^5 = \text{alkyl, CH}_2\text{SO}_2\text{CH}_3, \text{C}(\text{CH}_3)_2\text{SO}_2\text{CH}_3, \text{CH}_2\text{CONH}_2, \text{CH}_2\text{SCH}_3, \text{imidaz-4-ylmethyl, CH}_2\text{NHAc, CH}_2\text{NHCOCF}_3, \text{tert-butyl}$

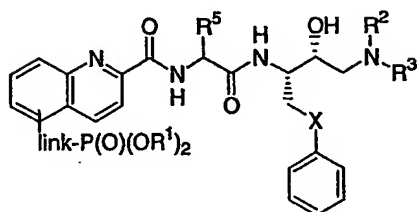
Chart 2



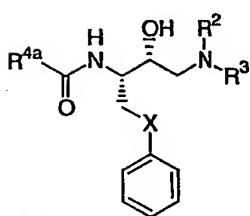
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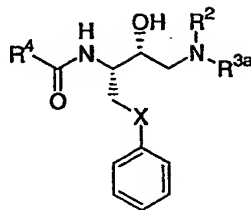
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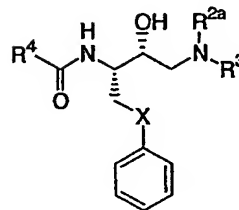
10



11



12



13

R^{4a} = phosphonate containing R⁴ R^{3a} = phosphonate containing R³ R^{2a} = phosphonate containing R²

R¹ = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

X = S or direct bond

R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

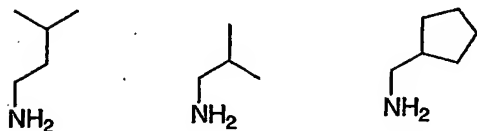
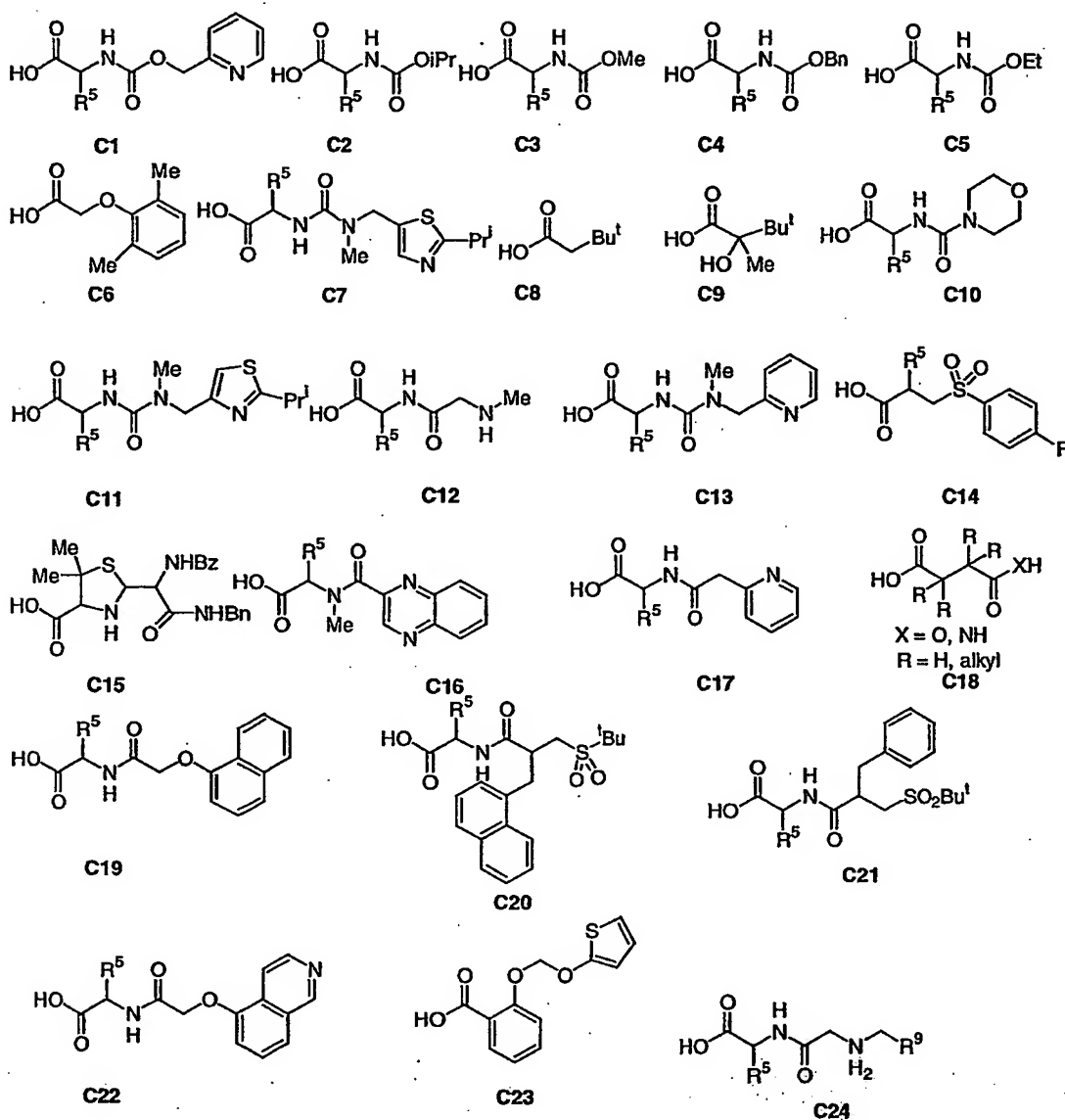
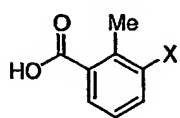
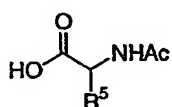
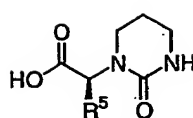
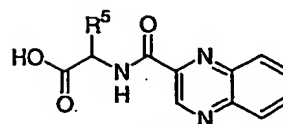
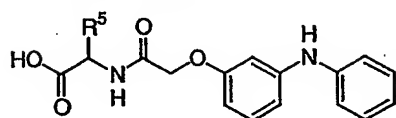
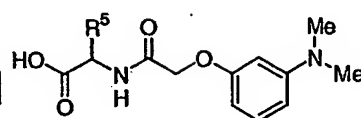
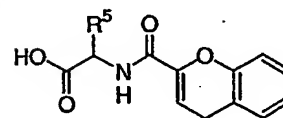
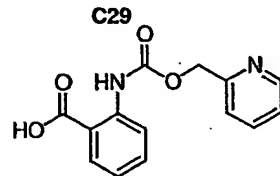
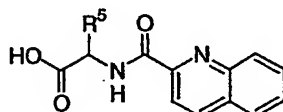
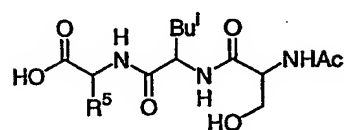
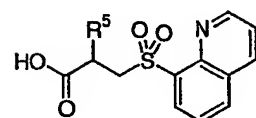
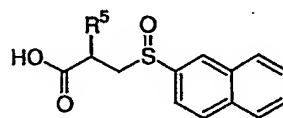
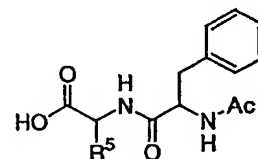
Chart 3 Structures containing the R²-NH₂ components**Chart 4 Structures containing the R³-Cl components**

Chart 5a Structures of the R⁴COOH components

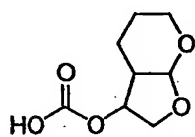
R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc,
 CH₂NHCOCF₃, tert-butyl

Chart 5b Structures of the R⁴COOH components

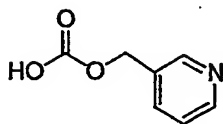
C25
X = OH, NH₂

**C26****C27****C28****C29****C30****C31****C32****C33****C34****C35****C36****C37**

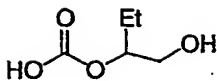
R⁵ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃, tert-butyl

Chart 5c Structures of the R⁴COOH components

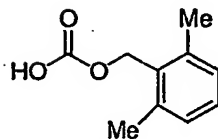
C38



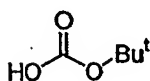
C39



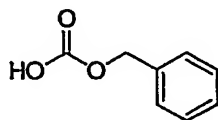
C40



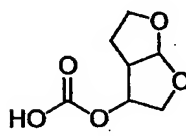
C41



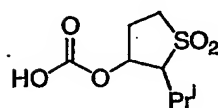
C42



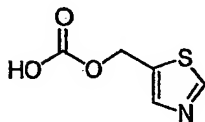
C43



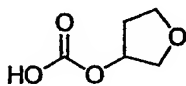
C44



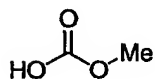
C45



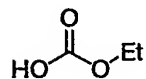
C46



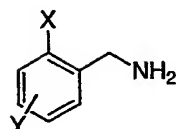
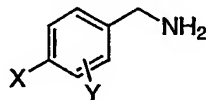
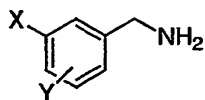
C47



C48



C49

Chart 6 Structures of the R⁹CH₂NH₂ components

X = F, Br, Cl ; Y = H, F, Br, Cl

Chart 7

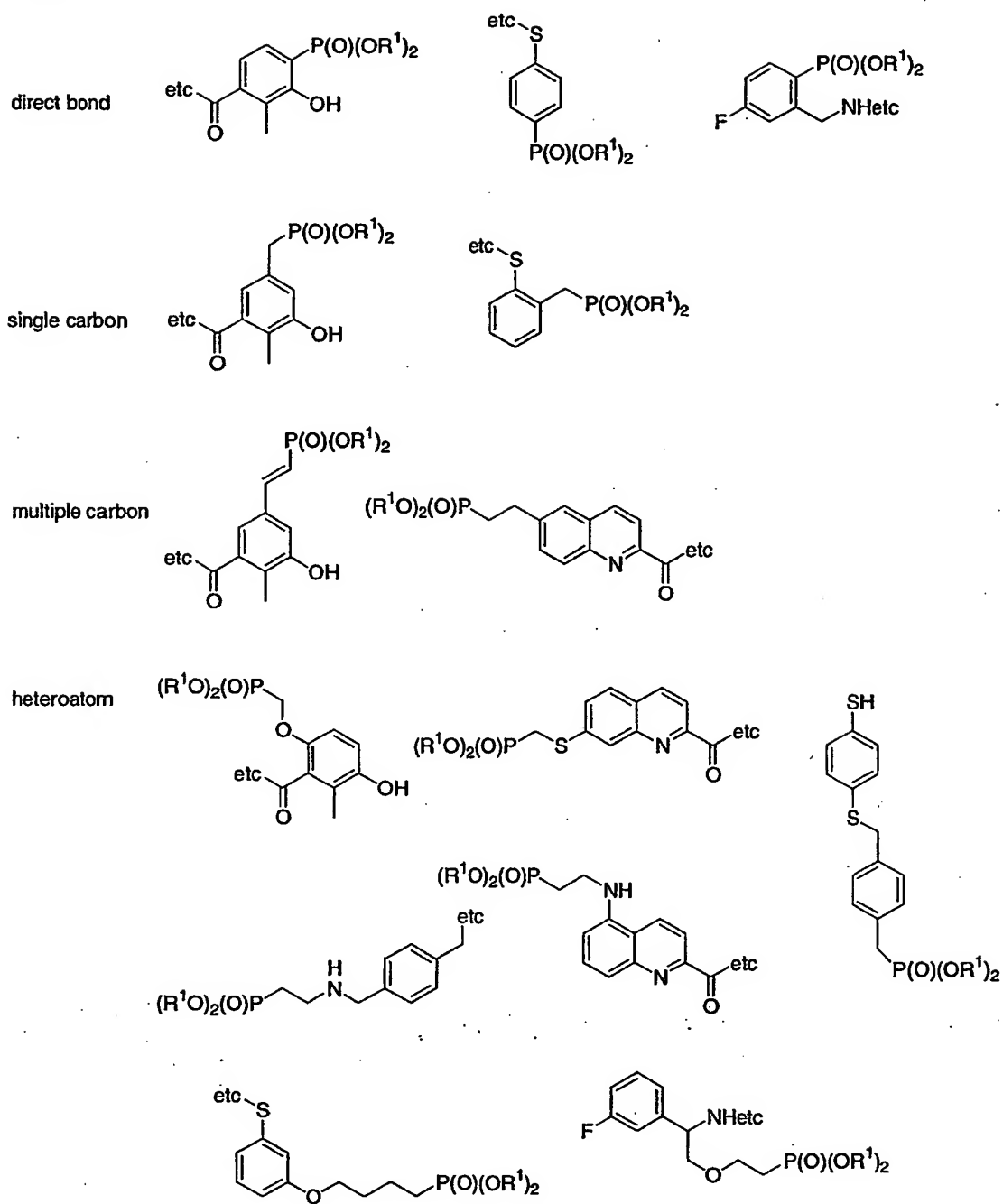
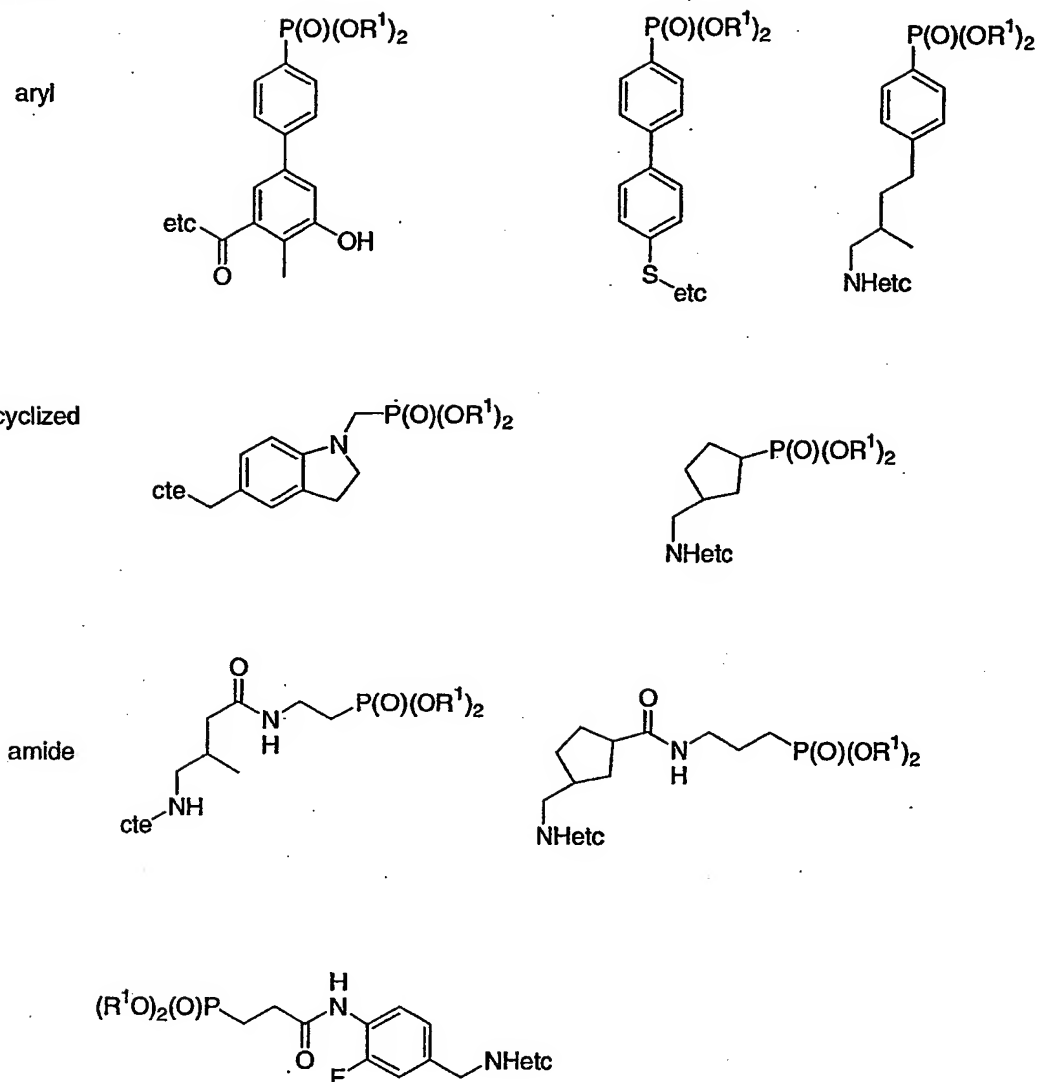


Chart 8



Protection of reactive substituents.

- 5 Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990
- 10 or Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

The intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the R₄COOH group does not contain an secondary amine, and in which the substituent A is
5 either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc are prepared as shown in Schemes 1-2. The epoxide 1.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br is prepared as described in Schemes 56-59 below. Treatment of the epoxide 1.1 with the amine 1.2 affords the aminoalcohol 1.3. The preparation of aminoalcohols by reaction between an amine and an
10 epoxide is described, for example, in Advanced Organic Chemistry, by J. March, McGraw Hill, 1968, p 334. In a typical procedure, equimolar amounts of the reactants are combined in a polar solvent such as an alcohol or dimethylformamide and the like, at from ambient to about 100°, for from 1 to 24 hours, to afford the product 1.3. The amino alcohol 1.3 is then treated with an acylating agent 1.4 to afford the product 1.5. The acylating agent is typically a
15 chloroformate or a sulfonyl chloride as shown in chart 4. Coupling conditions for amines with sulfonyl chlorides is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 603-615 or for chloroformates, p494ff. Preferably, the amine 1.3 is treated with the sulfonyl chloride 1.4 in the presence of a base such as pyridine, potassium carbonate etc and THF / water to give the product 1.5. Product 1.5 is
20 deprotected using conditions described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 503ff. Preferably, the BOC amine is treated with TFA in an aprotic solvent such as THF. Conversion to the amide 1.8 is performed using standard coupling conditions between an acid 1.7 and the amine. The preparation of amides from carboxylic acids and derivatives is described, for example, in
25 Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.
30 Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride or anhydride, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

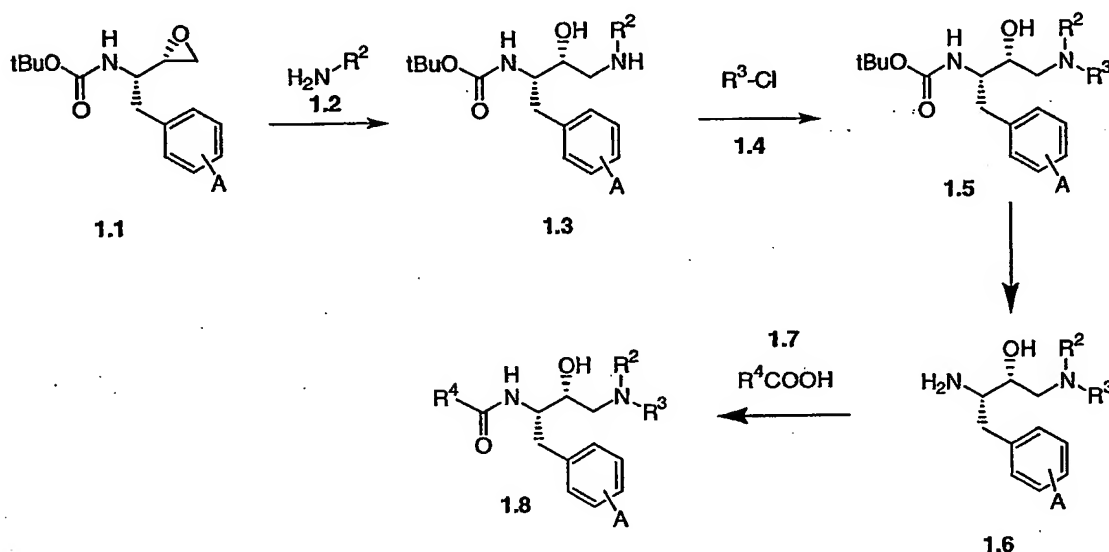
The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane.

Preferably, the carboxylic acid 1.7 is reacted with an equimolar amount of the amine 1.6 in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, in an aprotic solvent such as, for example, tetrahydrofuran, at about ambient temperature, so as to afford the amide product 1.8. The compound 1.8, and analogous acylation products described below, in which the carboxylic acid R^4COOH is one of the carbonic acid derivatives C38-C49, as defined in Chart 5c, are carbamates. Methods for the preparation of carbamates are described below, Scheme 98.

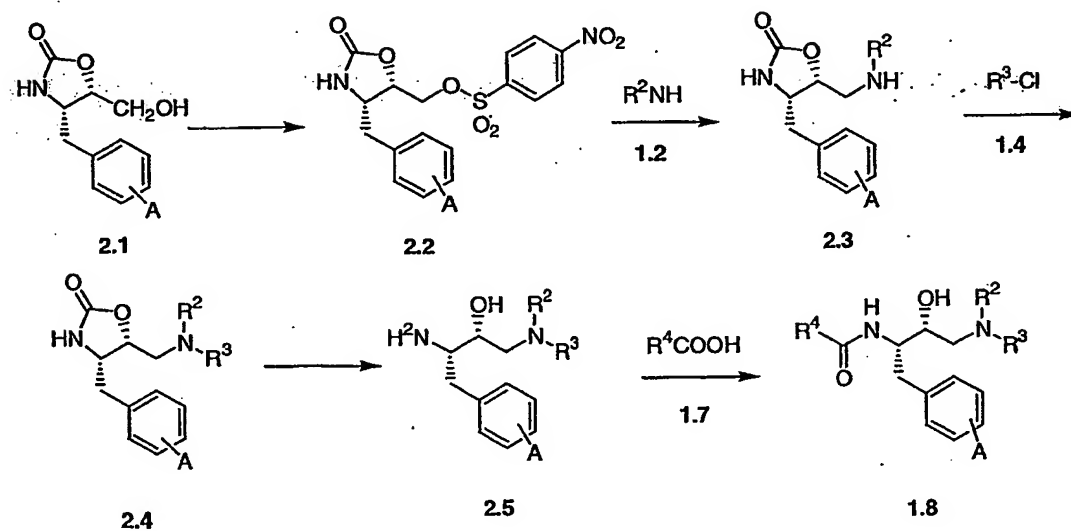
Scheme 2 illustrates an alternative method for the preparation of intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the R_4COOH group does not contain an secondary amine, and in which the substituent A is either the group link-
P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. The oxazolidinone 2.1, prepared as described in Schemes 60-62, is first activated as shown in 2.2 and then treated with amine 1.2 to afford the secondary amine 2.3. The hydroxyl group can be activated by converting into a bromo derivative, for example by reaction with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 92, 2139, 1970, or a methanesulfonyloxy derivative, by reaction with methanesulfonyl chloride and a base, or, preferably, into the 4-nitrobenzenesulfonyloxy derivative 2.2, by reaction in a solvent such as ethyl acetate or tetrahydrofuran, with 4-nitrobenzenesulfonyl chloride and a base such as triethylamine or N-methylmorpholine, as described in WO 9607642. The nosylate product 2.2 is then reacted with the amine component 1.2 to afford the displacement product 2.3. Equimolar amounts of the reactants are combined in an inert solvent such as dimethylformamide, acetonitrile or acetone, optionally in the presence of an organic or inorganic base such as triethylamine or sodium carbonate, at from about 0°C to 100°C to afford the amine product 2.3. Preferably, the reaction is performed in methyl isobutyl ketone at 80°C, in the presence of sodium carbonate, as described in WO 9607642. Treatment of the amine product 2.3 with the R3 chloride 1.4 as described in Scheme 1 then affords the product 2.4. The oxazolidinone group present in the product 2.4 is then hydrolyzed to afford the hydroxyamine 2.5. The hydrolysis reaction is effected in the presence of aqueous solution of a

- base such as an alkali metal hydroxide, optionally in the presence of an organic co-solvent. Preferably, the oxazolidinone compound 2.4 is reacted with aqueous ethanolic sodium hydroxide at reflux temperature, as described in WO 9607642, to afford the amine 2.5. This product is then reacted with the $R^4\text{COOH}$ carboxylic acid or activated derivative thereof, 1.7, to afford the product 1.8. The amide-forming reaction is conducted under the same conditions as described above, (Scheme 1).

Scheme 1



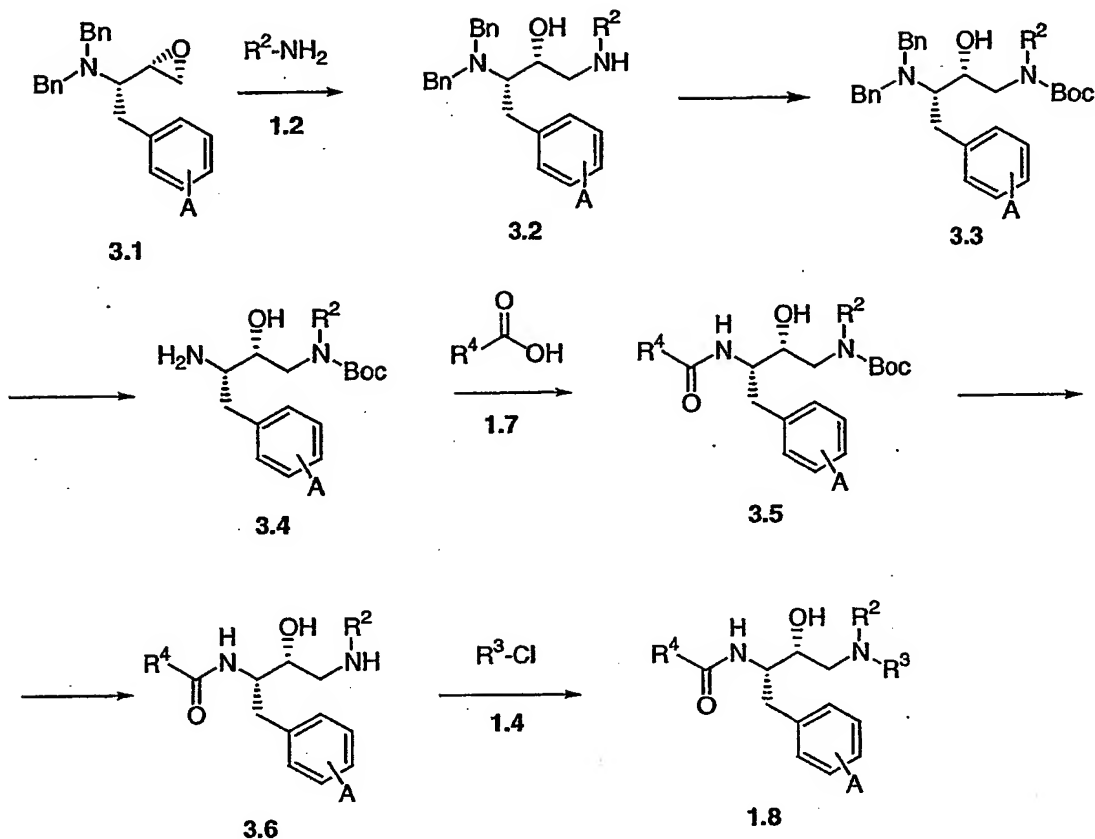
Scheme 2



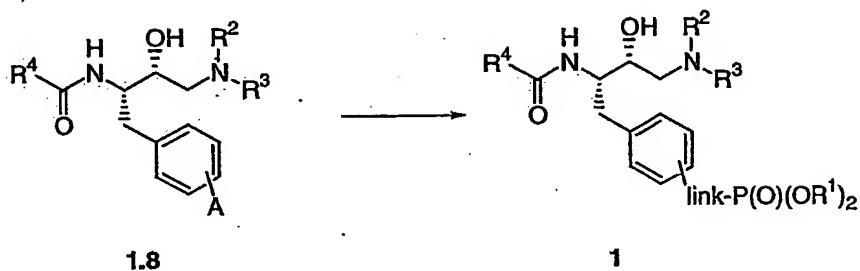
Scheme 3 illustrates the preparation of intermediate phosphonate esters 1, in which the group A is attached to the aryl moiety, the $R_4\text{COOH}$ group contains an secondary amine, and in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. The dibenzyl amine 3.2 is prepared from epoxide 3.1 and amine 1.2 ,
5 following the same procedures described in Scheme 1 for the preparation of 1.3. Epoxide 3.1 is prepared as described below in Schemes 56a. The amine 3.2 is then converted to the amine 3.4 as described in US6391919. Preferably, the amine is first protected as the BOC carbamate and then treated with palladium hydroxide on carbon (20%) in methanol under hydrogen at high pressure to give the amine 3.4. Treatment of 3.4 with the $R_4\text{COOH}$ acid 1.7 which
10 contains a secondary or primary amine, under standard amide bond forming conditions as described above, Scheme 1, then affords the amide 3.5. Preferably, the acid 1.7, EDC and *n*-hydroxybenzotriazole in DMF is treated with the amine 3.4 to give the amide 3.5. Removal of the BOC group as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 520-525 then affords the amine 3.6. Preferably
15 the BOC amine 3.5 is treated with HCl in dioxane and water to give the free amine 3.6. The amine 3.6 is then treated with an acylating agent such as an acid, chloroformate or sulfonyl chloride to give the final product 1.8. Standard coupling conditions for amines with acids or sulfonyl chlorides is indicated above Scheme 1. Preferably, the amine 3.6 is treated with nitro-sulfonyl chloride in THF and water in the presence of a base such as potassium carbonate
20 to give the sulfonamide 1.8.

The reactions shown in Scheme 1-3 illustrate the preparation of the compound 1.8 in which the substituent A is either the group link- $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 4 depicts the conversion of 1.8 in which A is [OH], [SH], [NH], Br etc,
25 into the phosphonate ester 1 in which X is a direct bond. In this procedure 1.8 is converted, using the procedures described below, Schemes 47-99, into the compound 1. Also, in the preceding and following Schemes, the amino substituted sulfonamide reagents are typically introduced as a nitro-sulfonamide reagents. Therefore, where appropriate, an additional step of nitro group reduction as described in Comprehensive Organic Transformations, by R. C.
30 Larock, 2nd Edition, 1999, p.821ff, is performed to give the final amino products.

Scheme 3



Scheme 4



Scheme 5 illustrates an alternative method for the preparation of the compound 1 in which the group A is attached to the aryl moiety, the R_4COOH group contains a primary or secondary amine and in which the substituent A is either the group $link-P(O)(OR^1)_2$ or a precursor such as $[OH]$, $[SH]$, $[NH]$, Br etc. The amine 3.4, (Scheme 3) is treated with an amino acid 5.1

under typical amide bond forming conditions to give the amide 5.2 as described above, Scheme 1. Preferably the acid 5.1 is first treated with EDC and n-hydroxybenzotriazole in DMF and then the amine 3.4 is added in DMF followed by N-methyl morpholine to give the amide 5.2. Reduction of the amide under the same catalytic hydrogenation conditions as described above in Scheme 3 gives the free amine 5.3. The amine is further treated with chloroacetyl chloride to provide the chloro compound 5.4. Preferably treatment with the chloroacetyl chloride is performed in ethyl acetate and water mixture in the presence of a base such as potassium hydrogen carbonate. The chloro compound 5.4 is treated with hydrochloric acid in dioxane and ethyl acetate to give the salt of the free amine 5.5. The salt 5.5 is then treated with a nitro-sulfonyl chloride 1.4 in THF and water in the presence of a base such as potassium carbonate to give the sulfonamide 5.6. Alternatively the free amine 5.5 is treated with a chloroformate 1.4 in the presence of a base such as triethylamine to afford the carbamate. Methods for the preparation of carbamates are also described below, Scheme 98. Compound 5.6 is then treated with the amine 5.7 to give the secondary amine 5.8. Preferably the chloride is refluxed in the presence of the amine 5.7 in THF.

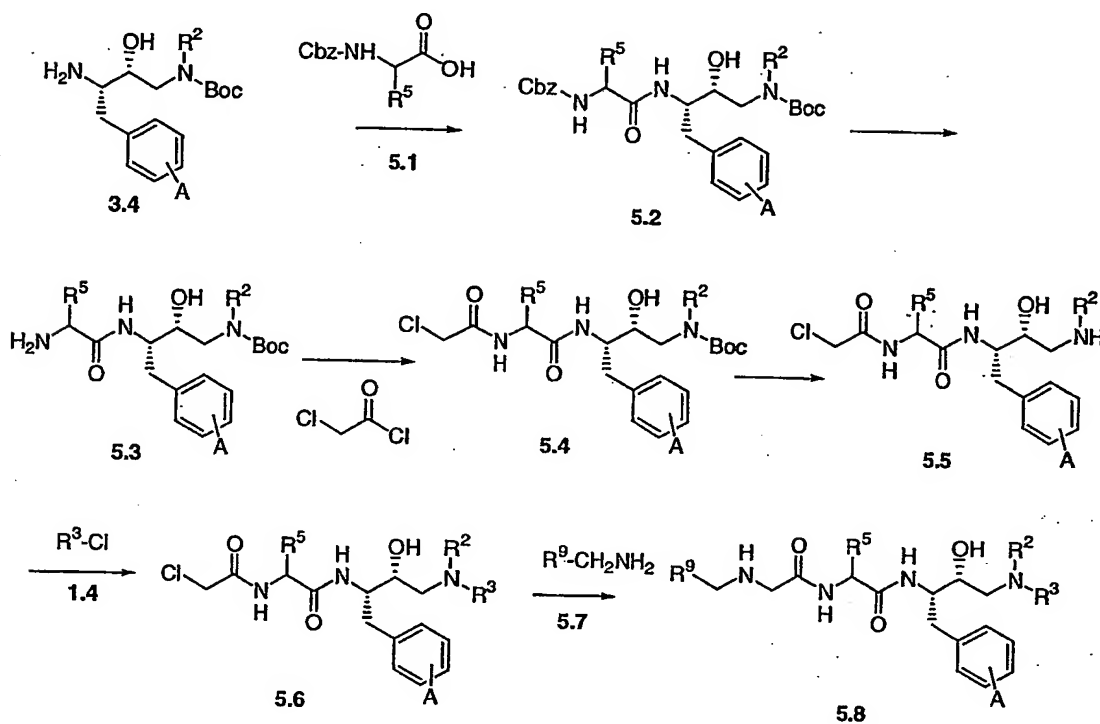
The reactions shown in Scheme 5 illustrate the preparation of the compound 5.8 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 6 depicts the conversion of 5.8 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 1 in which X is a direct bond. In this procedure 5.8 is converted, using the procedures described below, Schemes 47-99, into the compound 1.

In the preceding and following schemes, the conversion of various substituents into the group $\text{link-P(O)(OR}^1)_2$ can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, during the introduction of the group $\text{link-P(O)(OR}^1)_2$.

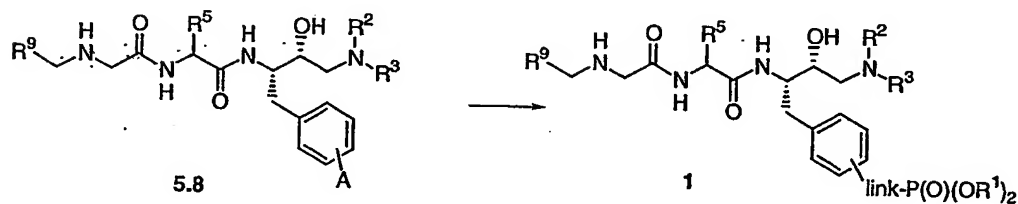
In the preceding and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical

transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 99).

Scheme 5



Scheme 6



5

Preparation of the phosphonate ester intermediates 1 in which X is a sulfur.

The intermediate phosphonate esters 1, in which X is sulfur, the R₄COOH group does not contain a amine group, and in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, are prepared as shown in Schemes 7-9.

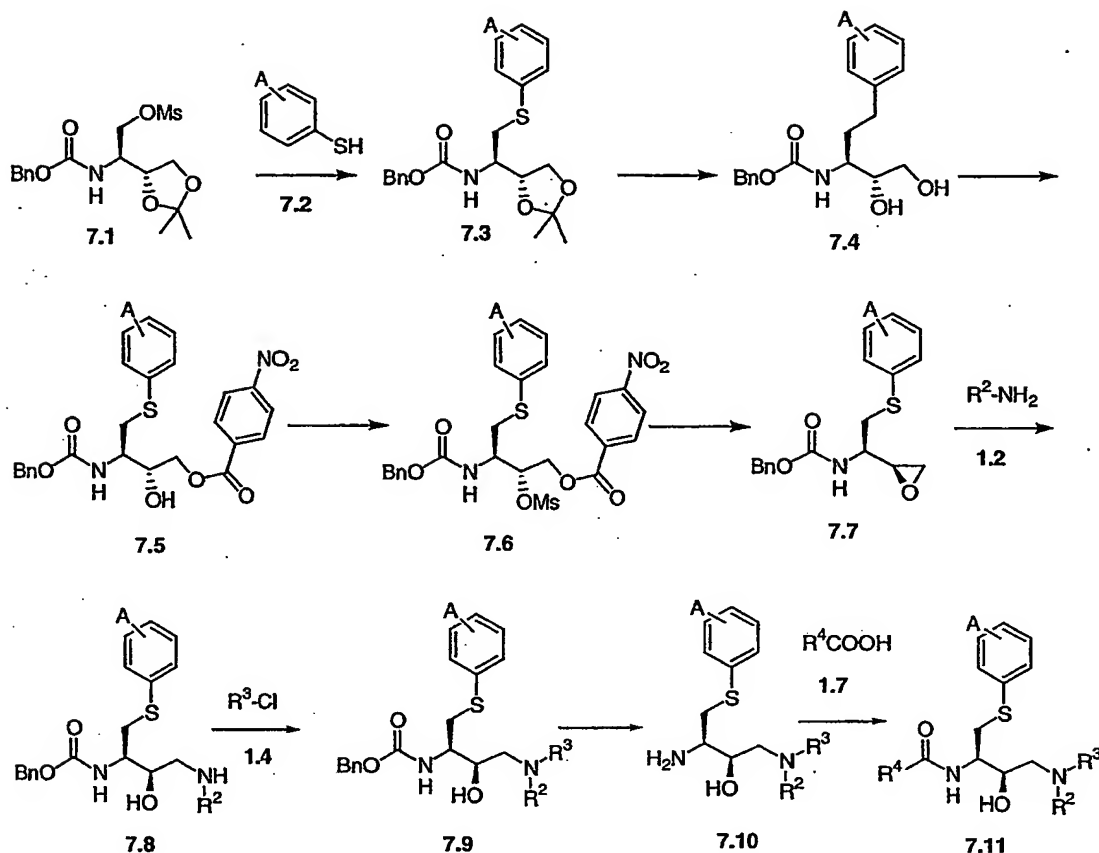
10

Scheme 7 illustrates one method for the preparation of the compounds 1 in which the substituent X is S, and in which the group A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, methanesulfonic acid 2-benzoyloxycarbonylamino-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-ethyl ester, 7.1, prepared as described in J. Org. Chem, 2000, 65, 1623, is reacted with a thiol 7.2 to afford the thioether 7.3. The preparation of thiol 7.2 is described in Schemes 63-72. The reaction is conducted in a suitable solvent such as, for example, pyridine, DMF and the like, in the presence of an inorganic or organic base, at from 0°C to 80°C, for from 1-12 hours, to afford the thioether 7.3. Preferably the mesylate 7.1 is reacted with an equimolar amount of the thiol, in a mixture of a water-immiscible organic solvent such as toluene, and water, in the presence of a phase-transfer catalyst such as, for example, tetrabutyl ammonium bromide, and an inorganic base such as sodium hydroxide, at about 50°C, to give the product 7.3. The 1,3-dioxolane protecting group present in the compound 7.3 is then removed by acid catalyzed hydrolysis or by exchange with a reactive carbonyl compound to afford the diol 7.4. Methods for conversion of 1,3-dioxolanes to the corresponding diols are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p191. For example, the 1,3-dioxolane compound 7.3 is hydrolyzed by reaction with a catalytic amount of an acid in an aqueous organic solvent mixture. Preferably, the 1,3-dioxolane 7.3 is dissolved in aqueous methanol containing hydrochloric acid, and heated at ca. 50°C, to yield the product 7.4. The primary hydroxyl group of the diol 7.4 is then selectively acylated by reaction with an electron-withdrawing acyl halide such as, for example, pentafluorobenzoyl chloride or mono- or di-nitrobenzoyl chlorides. The reaction is conducted in an inert solvent such as dichloromethane and the like, in the presence of an inorganic or organic base. Preferably, equimolar amounts of the diol 7.4 and 4-nitrobenzoyl chloride are reacted in a solvent such as ethyl acetate, in the presence of a tertiary organic base such as 2-picoline, at ambient temperature, to afford the hydroxy ester 7.5. The hydroxy ester is next reacted with a sulfonyl chloride such as methanesulfonyl chloride, 4-toluenesulfonyl chloride and the like, in the presence of a base, in an aprotic polar solvent at low temperature, to afford the corresponding sulfonyl ester 7.6. Preferably, equimolar amounts of the carbinol 7.5 and methanesulfonyl chloride are reacted together in ethyl acetate containing triethylamine, at about 10°C, to yield the mesylate 7.6. The compound 7.6 is then subjected to a hydrolysis-

cyclization reaction to afford the oxirane 7.7. The mesylate or analogous leaving group present in 7.6 is displaced by hydroxide ion, and the carbinol thus produced, without isolation, spontaneously transforms into the oxirane 7.7 with elimination of 4-nitrobenzoate. To effect this transformation, the sulfonyl ester 7.6 is reacted with an alkali metal hydroxide or
5 tetraalkylammonium hydroxide in an aqueous organic solvent. Preferably, the mesylate 7.6 is reacted with potassium hydroxide in aqueous dioxan at ambient temperature for about 1 hour, to afford the oxirane 7.7.

The oxirane compound 7.7 is then subjected to regiospecific ring-opening reaction by treatment with a secondary amine 1.2, to give the aminoalcohol 7.8. The amine and the
10 oxirane are reacted in a protic organic solvent, optionally in the additional presence of water, at 0°C to 100°C, and in the presence of an inorganic base, for 1 to 12 hours, to give the product 7.8. Preferably, equimolar amounts of the reactants 7.7 and 1.2 are reacted in aqueous methanol at about 60°C in the presence of potassium carbonate, for about 6 hours, to afford the aminoalcohol 7.8. The free amine is then substituted by treatment with an acid,
15 chloroformate or sulfonyl chloride as described above in Scheme 1 to give the amine 7.9. The carbobenzyloxy (cbz) protecting group in the product 7.9 is removed to afford the free amine 7.10. Methods for removal of cbz groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition, p. 335. The methods include catalytic hydrogenation and acidic or basic hydrolysis. For example, the cbz-protected
20 amine 7.9 is reacted with an alkali metal or alkaline earth hydroxide in an aqueous organic or alcoholic solvent, to yield the free amine 7.10. Preferably, the cbz group is removed by the reaction of 7.9 with potassium hydroxide in an alcohol such as isopropanol at ca. 60°C to afford the amine 7.10. The amine 7.10 so obtained is next acylated with a carboxylic acid or activated derivative 1.7, using the conditions described above in Scheme 1 to afford the
25 product 7.11

Scheme 7



Scheme 8 illustrates an alternative preparation of the compounds 1 in which the substituent X is S; and in which the group A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. In this sequence, 4-amino-tetrahydro-furan-3-ol, 8.1, the preparation of which is described in Tet. Lett., 2000, 41, 7017, is reacted with a carboxylic acid or activated derivative thereof, R⁴COOH, 1.7, using the conditions described above for in Scheme 1 for the preparation of amides, to afford the amide 8.2. The amide product 8.2 is then transformed, using the sequence of reactions shown in Scheme 8, into the isoxazoline compound 8.5. The hydroxyl group on the tetrahydrofuran moiety in 8.2 is converted into a leaving group such as p-toluenesulfonyl or the like, by reaction with a sulfonyl chloride in an aprotic solvent such as pyridine or dichloromethane. Preferably, the hydroxy amide 8.2 is reacted with an equimolar amount of methanesulfonyl chloride in pyridine, at ambient temperature, to afford the methanesulfonyl ester 8.3. The product 8.3, bearing a suitable sulfonyl ester leaving group, is then subjected to acid-catalyzed rearrangement to afford the isoxazoline 8.4. The

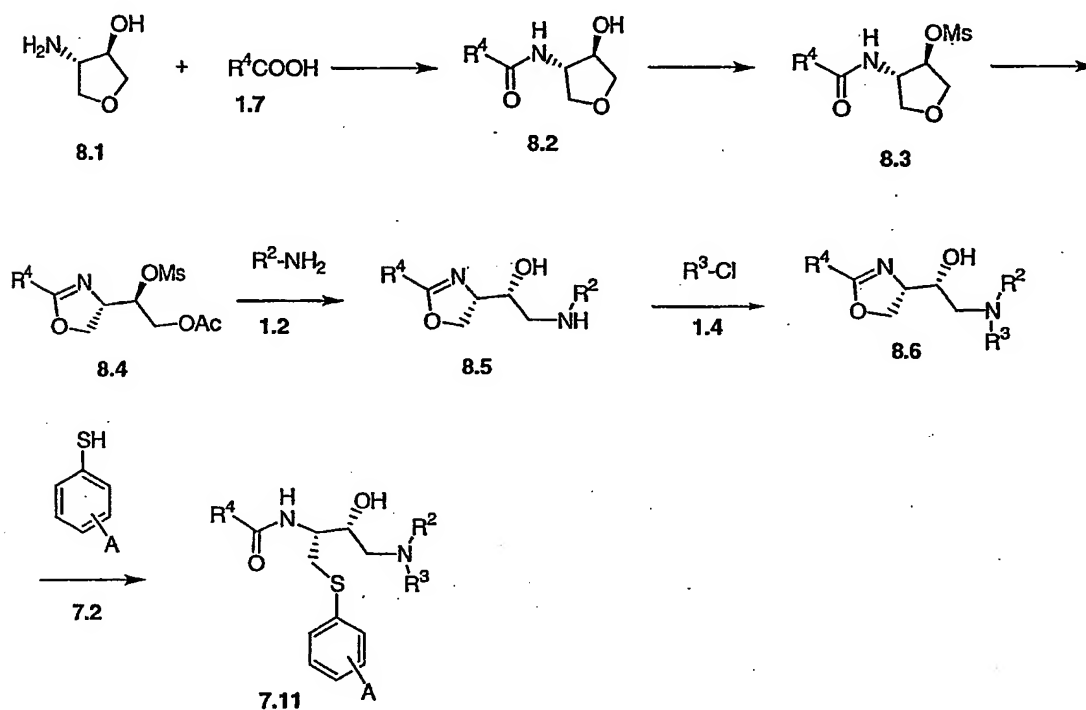
rearrangement reaction is conducted in the presence of an acylating agent such as a carboxylic anhydride, in the presence of a strong acid catalyst. Preferably, the mesylate 8.3 is dissolved in an acylating agent such as acetic anhydride at about 0°C, in the presence of about 5 mole % of a strong acid such as sulfuric acid, to afford the isoxazoline mesylate 8.4. The leaving group, for example a mesylate group, is next subjected to a displacement reaction with an amine. The compound 8.4 is reacted with an amine 1.2, as defined in Chart 3, in a protic solvent such as an alcohol, in the presence of an organic or inorganic base, to yield the displacement product 8.5. Preferably, the mesylate compound 8.4 is reacted with an equimolar amount of the amine 1.2, in the presence of an excess of an inorganic base such as potassium carbonate, at ambient temperature, to afford the product 8.5. The product 8.5 is then treated with R³Cl, chart 6 as described above in Scheme 1 to afford the amine 8.6. The compound 8.6 is then reacted with a thiol 7.2 to afford the thioether 7.11. The reaction is conducted in a polar solvent such as DMF, pyridine or an alcohol, in the presence of a weak organic or inorganic base, to afford the product 7.11. Preferably, the isoxazoline 8.6 is reacted, in methanol, with an equimolar amount of the thiol 7.2, in the presence of an excess of a base such as potassium bicarbonate, at ambient temperature, to afford the thioether 7.11.

The procedures illustrated in Scheme 7-8 depict the preparation of the compounds 7.11 in which X is S, and in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc, as described below. Scheme 9 illustrates the conversion of compounds 7.11 in which A is a precursor to the group link-P(O)(OR¹)₂ into the compounds 1 in which X=S. Procedures for the conversion of the substituent A into the group link-P(O)(OR¹)₂ are illustrated below, (Schemes 47 – 99).

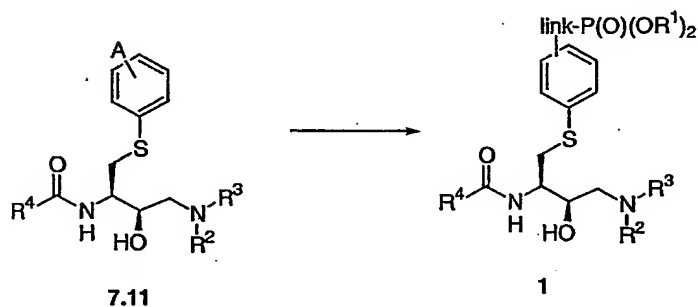
Scheme 9a-9b depicts the preparation of phosphonate esters 1, in which X is sulfur, the R₄COOH group does contain a amine group, and in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. The amine 7.10 prepared in Scheme 7 is treated with the CBZ protected amine 5.1 using the same conditions described in Scheme 5 for the preparation of 5.2 to give CBZ amine 9a.1. Removal of the CBZ group as described in Scheme 5 to give 9a.2 followed by treatment with chloroacetyl chloride as described in Scheme 5 gives chloride 9a.3. The chloride 9a.3 is then treated with the amine 5.7 to give the amine 9a.4 as described in Scheme 5.

The reactions shown in Scheme 9a illustrate the preparation of the compound 9a.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 9b depicts the conversion of 9a.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 1 in which X is sulfur. In this procedure 9a.4 is converted, using the procedures described below, Schemes 47-99, into the compound 1.

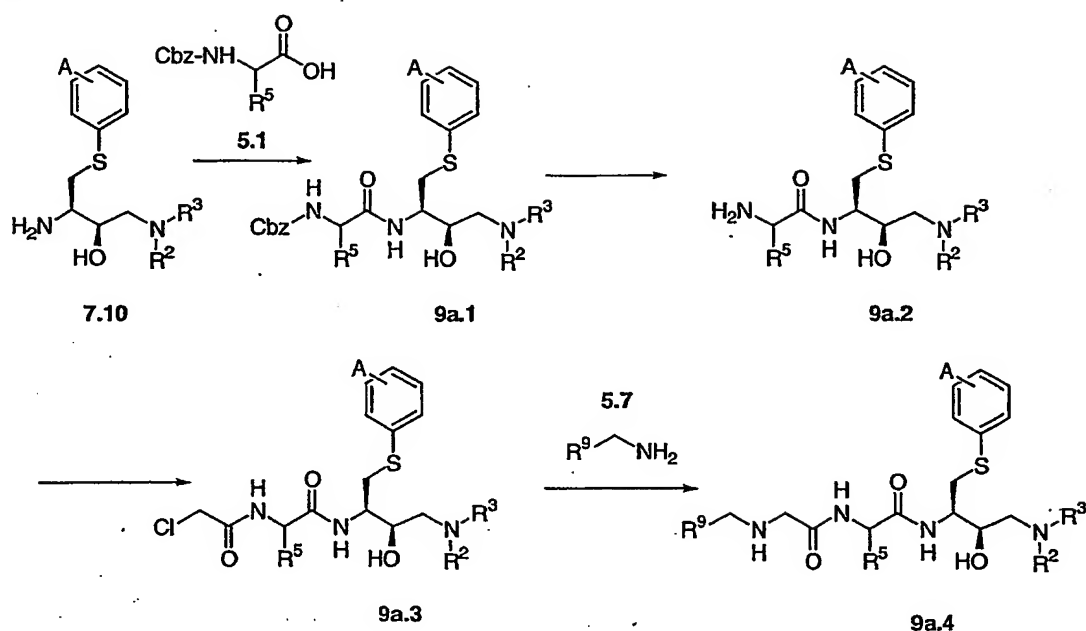
Scheme 8



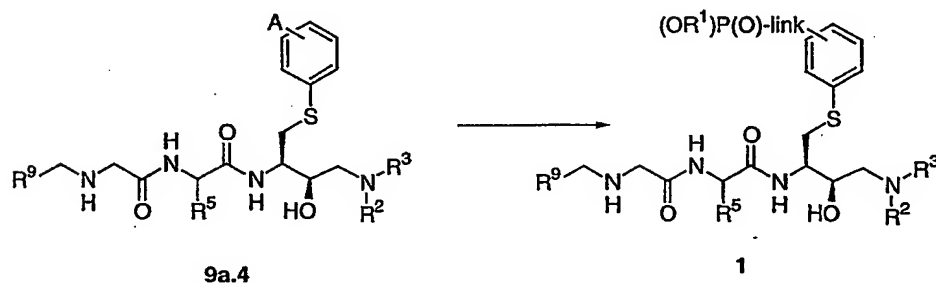
Scheme 9



Scheme 9a



Scheme 9b



Preparation of the phosphonate ester intermediates 2 and 3 in which X is a direct bond

5

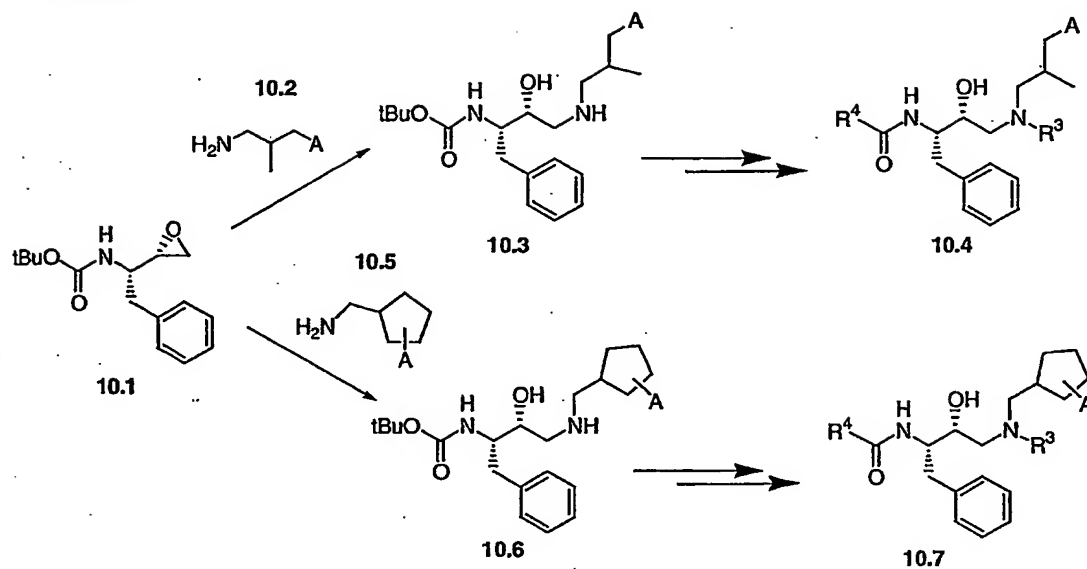
Schemes 10-12 illustrate the preparation of the phosphonate esters 2 and 3 in which X is a direct bond and the R_4COOH group does not contain a primary or secondary amine group. As shown in Scheme 10, the epoxide 10.1, prepared as described in J. Med. Chem 1994, 37, 1758 is reacted with the amine 10.2 or 10.5, in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amine 10.3 and 10.6 respectively. The reaction is performed under the same conditions as described

above, Scheme 1 for the preparation of the amine 1.3. The preparation of the amines 10.2 is described in Schemes 73-75 and amines 10.5 in schemes 76-78. The products 10.3 and 10.6 are then transformed, using the sequence of reactions described above, Scheme 1, for the conversion of the amine 1.3 into the amide 1.8, into the aminoamide 10.4 and 10.7 respectively.

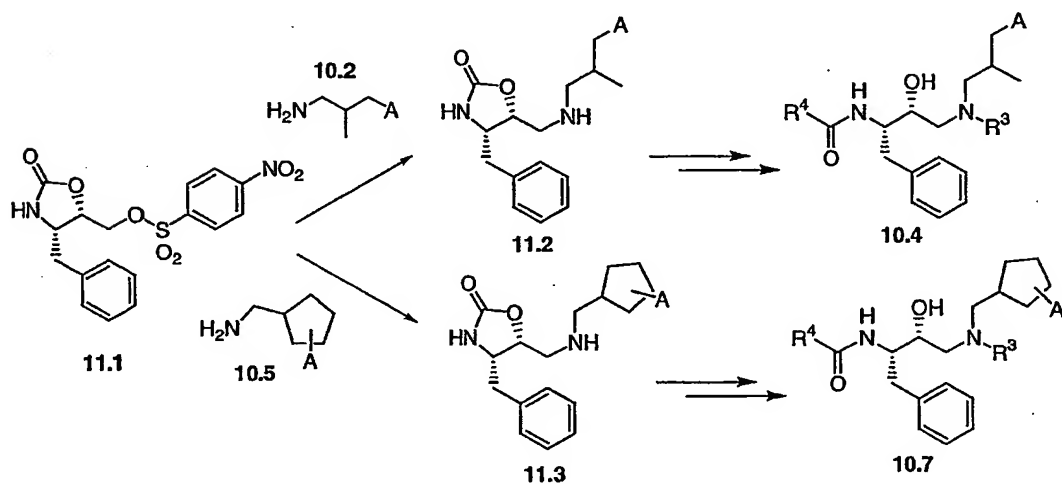
An alternative route to the amines 10.4 and 10.7 is shown in Scheme 11 in which sulfonyl ester 11.1 prepared according to Chimia 1996, 50, 532 is treated under conditions described in Scheme 2 with the amines 10.2 or 10.5 to give the amines 11.2 or 11.3 respectively. These amine products are then converted as described above, Scheme 2, into the amides 10.4 and 10.7 respectively.

The reactions shown in Scheme 10 and 11 illustrate the preparation of the compounds 10.4 and 10.7 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 12 depicts the conversion of these compounds 10.4 and 10.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2 and 3 respectively, in which X is a direct bond. In this procedure, the amines 10.4 and 10.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3 respectively.

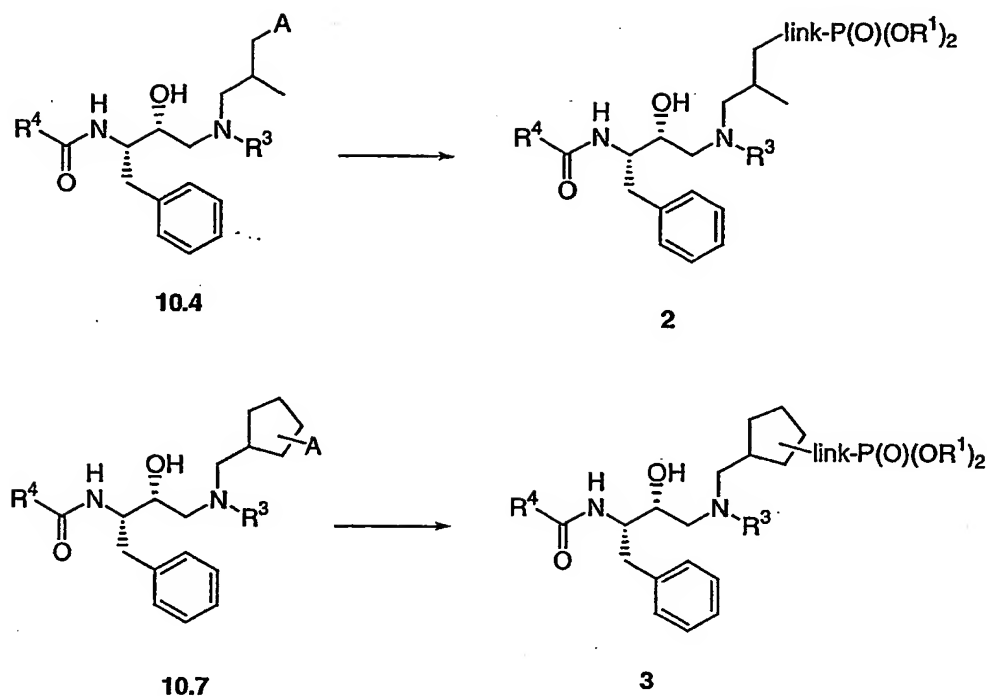
Scheme 10



Scheme 11



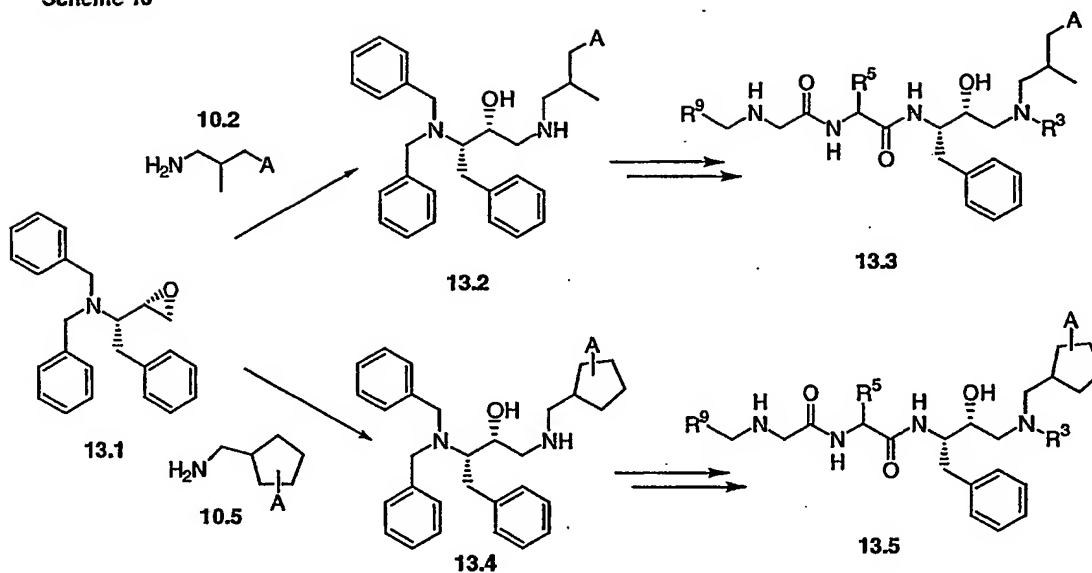
Scheme 12



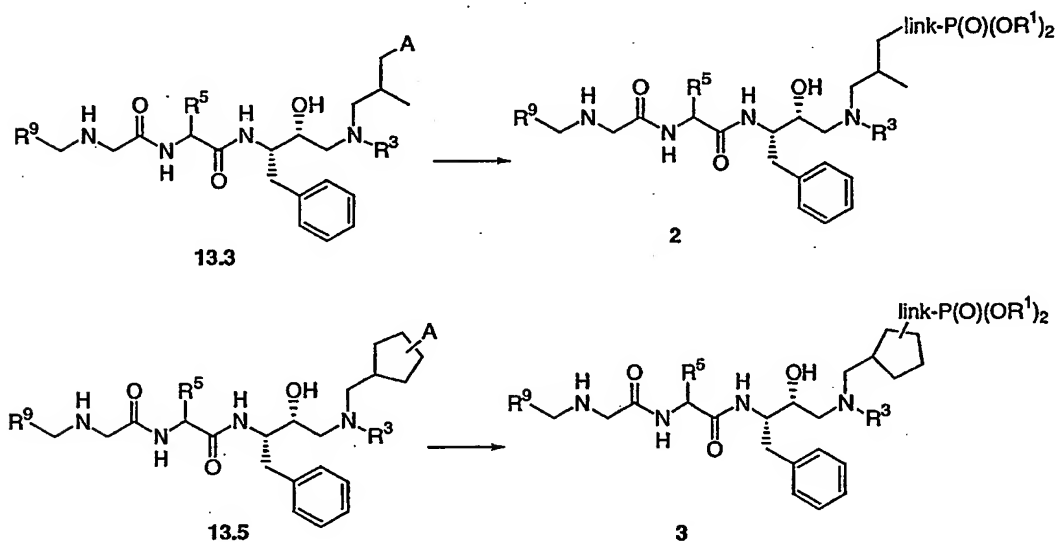
Schemes 13-14 illustrates the preparation of the phosphonate esters 2 and 3 in which X is a direct bond and the R_4COOH group contains an amine. The epoxide 13.1, prepared as described in US 6391919B1, or J. Org. Chem. 1996, 61, 3635 is reacted, as described above, (Scheme 1) with the amine 10.2 or 10.5, in which substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, to give the amino alcohols 13.2 and 13.4, respectively. These amines are then converted as described in Scheme 3 for the conversion of 3.2 into 3.4 and Scheme 5 for the conversion of 3.4 into 5.8, into the amine products 13.3 and 13.5 respectively.

The reactions shown in Scheme 13 illustrate the preparation of the compounds 13.3 and 13.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 14 depicts the conversion of the compounds 13.3 and 13.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 2 and 3 in which X is a direct bond. In this procedure, the compounds 13.3 and 13.5 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3 respectively.

Scheme 13



Scheme 14



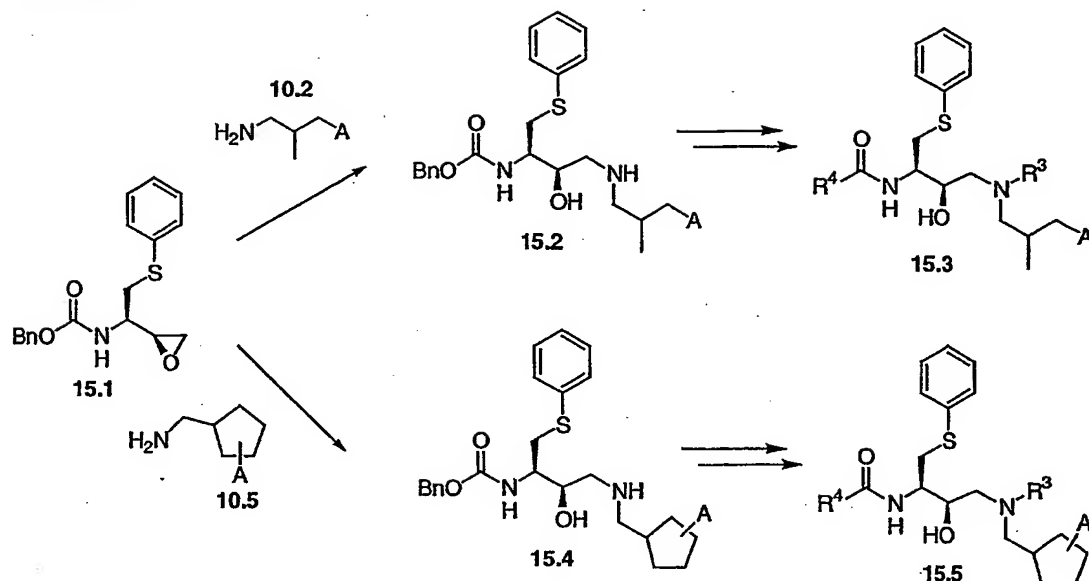
Preparation of the phosphonate ester intermediates 2 and 3 in which X is a sulfur

- 5 The intermediate phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group does not contain an amine group, are prepared as shown in Schemes 15-17. In Scheme 15, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 for the preparation of 7.7 from 7.1, except incorporating

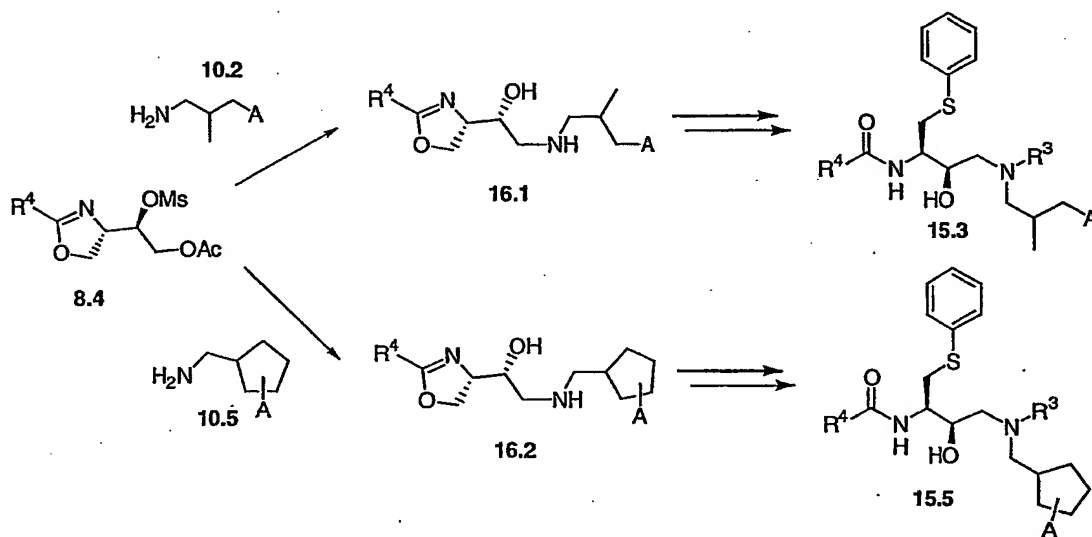
thiophenol for thiol 7.2. The epoxide 15.1 is then treated with amine 10.2 or amine 10.5, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amines 15.2 and 15.4. Further application of Scheme 7 on the amines 15.2 and 15.4 yields the alcohols 15.3 and 15.5 respectively.

- 5 Alternatively, Scheme 16 depicts the preparation of 15.3 and 15.5 using the mesylate 8.4. The amines 10.2 and 10.5 are reacted with mesylate 8.4 under conditions described in Scheme 8 to give amines 16.1 and 16.2 respectively. Further modification of 16.1 and 16.2 according to the conditions described in Scheme 8 then affords alcohols 15.3 and 15.5 respectively.
- 10 The reactions shown in Scheme 15-16 illustrate the preparation of the compounds 15.3 and 15.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 17 depicts the conversion of 15.3 and 15.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 in which X is sulfur. In this procedure 15.3 or 15.5 is converted, using the procedures described below, Schemes 47-99,
- 15 into the compound 2 and 3.

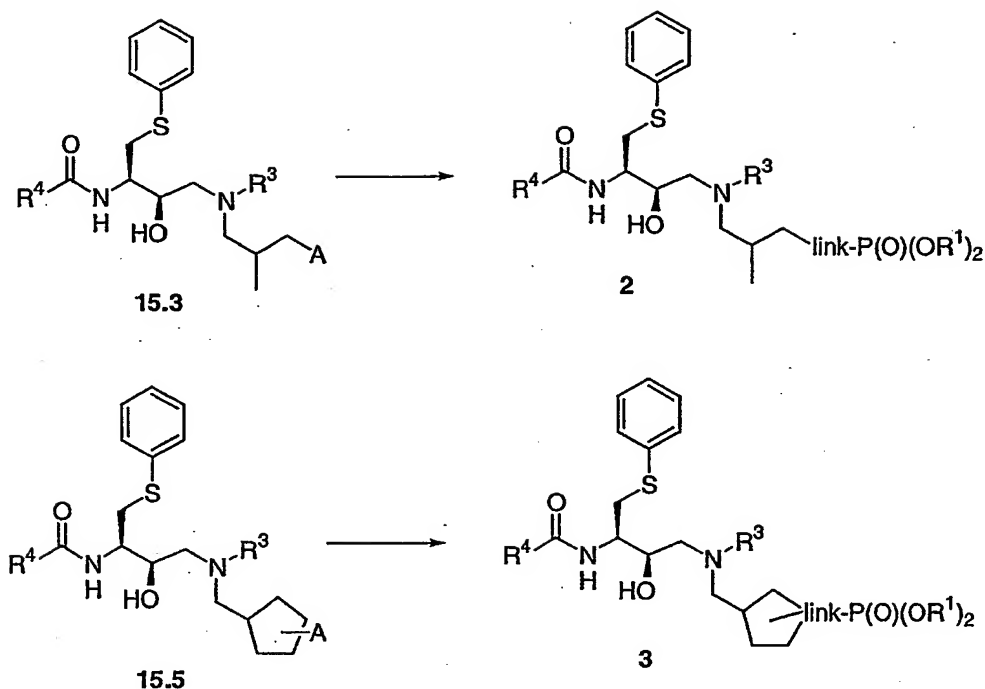
Scheme 15



Scheme 16

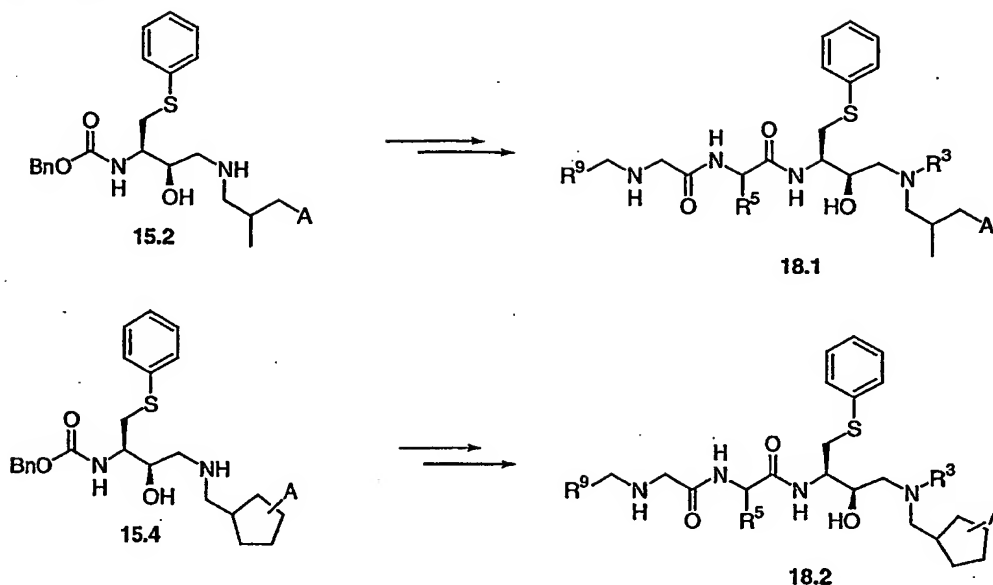


Scheme 17

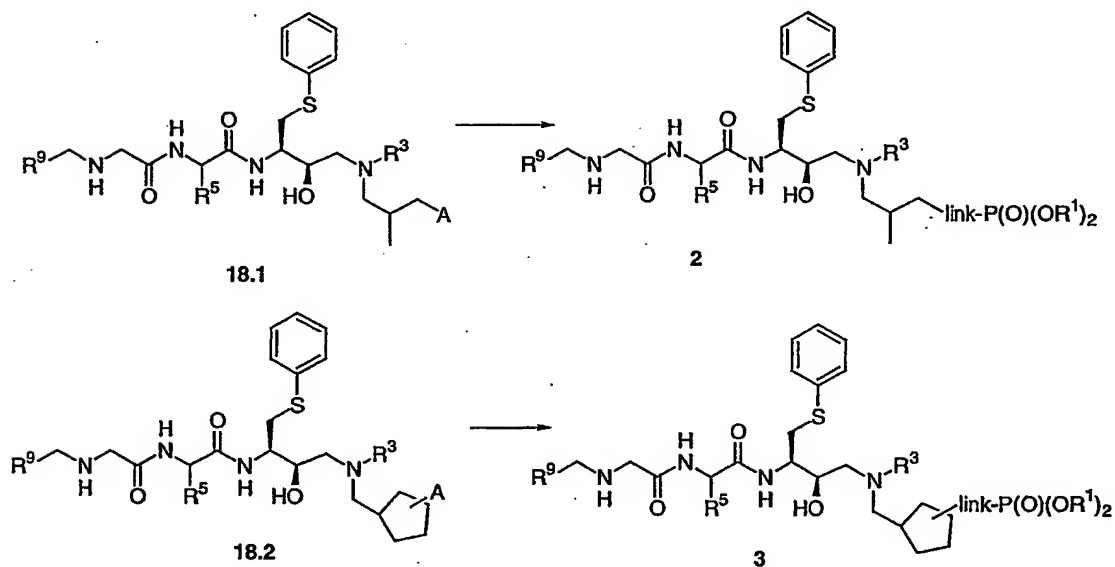


- Scheme 18-19 depict the preparation of phosphonate esters 2 and 3, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine group. The amines 15.2 and 15.4, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, prepared in Scheme 15, are converted using the same conditions described in Scheme 7 for the preparation of the amine 7.10 from 7.8 and Scheme 9a for the preparation of 9a.4 from 7.10 to give 18.1 and 18.2 respectively.
- The reactions shown in Scheme 18 illustrate the preparation of the compound 18.1 and 18.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 19 depicts the conversion of 18.1 and 18.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 2 and 3 respectively in which X is sulfur. In this procedure 18.1 and 18.2 are converted, using the procedures described below, Schemes 47-99, into the compounds 2 and 3

Scheme 18



Scheme 19



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond

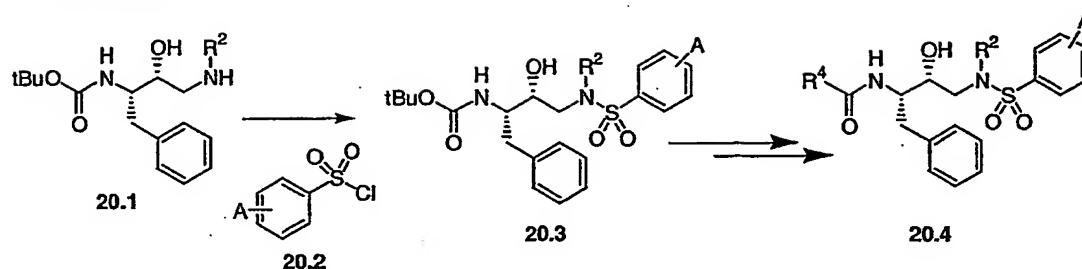
- 5 Schemes 20-22 illustrate the preparation of the phosphonate esters 4 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 20, the amine 20.1 is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, to

afford the product 20.3. The reaction is performed under the same conditions as described above, Scheme 1 for the preparation of the sulfonamide 1.5. Amine 20.1 is prepared by treatment of epoxide 10.1 with the amine 1.2 as described in Scheme 1 for the preparation of 1.3. The preparation of sulfonyl chloride 20.2 is described in Schemes 92-97. The product
5 20.3 is then transformed, using the sequence of reactions described above, Scheme 1, for the conversion of the amide 1.5 into the amide 1.8, into the product 20.4.

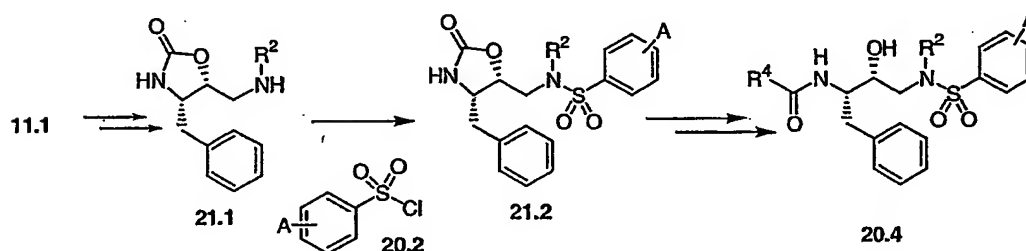
An alternative route to the product 20.4 is shown in Scheme 21 in which amine 11.1 is treated under conditions described in Scheme 2 with the amine 1.2 to give the amine 21.1. The amine
10 21.1 is then sulfonylated with 20.2 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 2, to afford the product 21.2. The product 21.2 is then converted as described above, Scheme 2, into the sulfonamide 20.4.

15 The reactions shown in Scheme 20 and 21 illustrate the preparation of the compound 20.4 in which the substituent A is either the group link- $P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 22 depicts the conversion of this compounds 20.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 4 respectively, in which X is a direct bond. In this procedure, the amines 20.4 is converted, using the procedures described below,
20 Schemes 47-99, into the compounds 4.

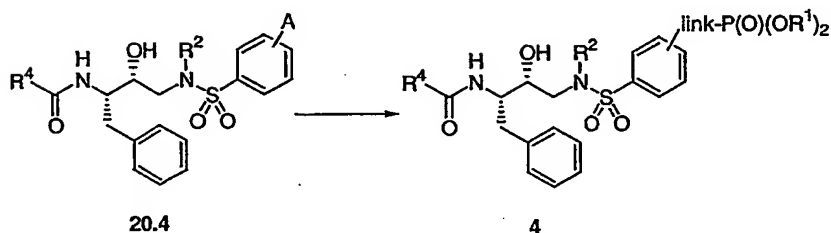
Scheme 20



Scheme 21



Scheme 22

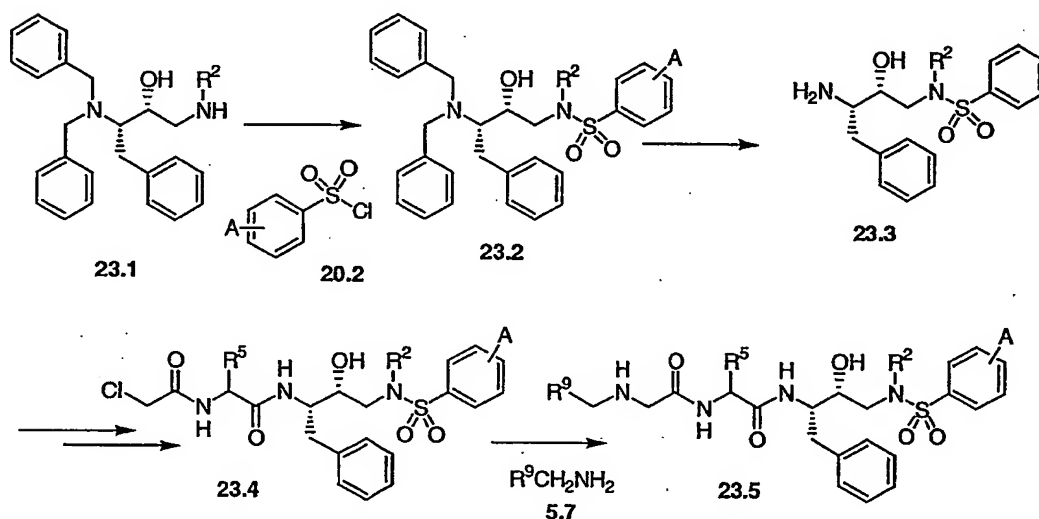


Schemes 23 illustrates the preparation of the phosphonate esters 4 in which X is a direct bond and the R₄COOH group contains an amine group. The amine 23.1, prepared from the epoxide 13.1 and an amine 1.2 as described in Scheme 13 for the synthesis of 13.2 from 13.1, is reacted with the sulfonyl chloride 20.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Schemes 1 for the synthesis of 1.5, to give the product 23.2. The product 23.2 is then reduced to amine 23.3 according to the conditions described in Scheme 3 for the preparation of 3.4 from 3.3. The amine product is then converted as described in Scheme 5 into the chloride 23.4. The chloride is treated with the amine 5.7 to afford the amine 23.5, as described in Scheme 5 for the preparation of 5.8 from 5.7.

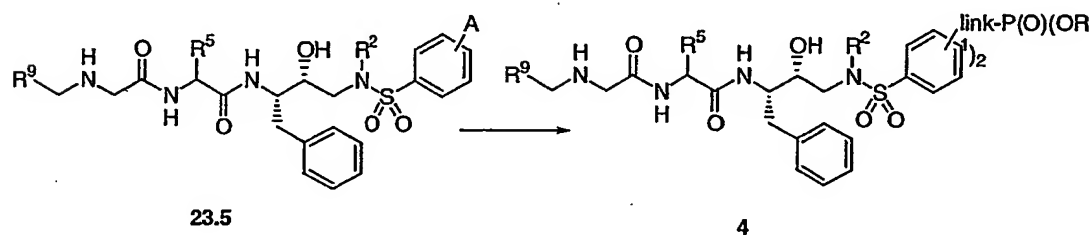
The reactions shown in Scheme 23 illustrate the preparation of the compound 23.5 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc. Scheme 24 depicts the conversion of the compound 23.5 in which A is $[\text{OH}]$, $[\text{SH}]$, $[\text{NH}]$, Br etc, into the phosphonate esters 4 in which X is a direct bond. In this

5 procedure, the compound 23.5 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

Scheme 23



Scheme 24



10 Preparation of the phosphonate ester intermediates 4 in which X is a sulfur

The intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R_4COOH group does not contain an amine is prepared as shown in Schemes 25-27. Amine 25.1 prepared from epoxide 15.1 and amine 1.2 as described in Scheme 15 is

5 treated with sulfonamide 20.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described in Scheme 7, to give the sulfonamide 25.2. The sulfonamide 25.2 is then converted as described in Scheme 7 for the conversion of 7.9 to 7.10, and Scheme 9a for the conversion of 7.10 into 9a.4, to the product 25.3. Alternatively, Scheme 26, illustrates how the amine 8.5 prepared according to Scheme 8 is reacted with 20.2 under conditions described in Scheme 8 for the preparation of 8.6 from 8.5, to give the sulfonamide 26.1. Further modification according to the conditions described in Scheme 8 for the preparation of 7.11, affords sulfonamide 25.3.

10 The reactions shown in Scheme 25-26 illustrate the preparation of the compounds sulfonamide 25.3 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 27 depicts the conversion of 25.3 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 4 in which X is sulfur. In this procedure 25.3 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

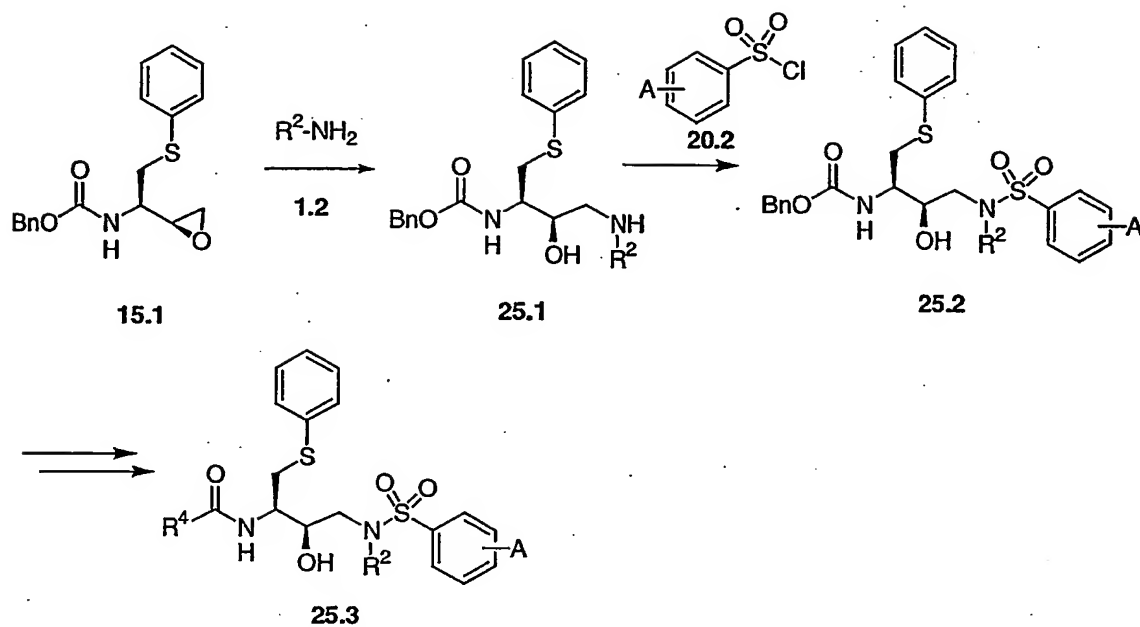
15 Preparation of the intermediate phosphonate ester 4, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine are prepared as shown in Schemes 28-29. Amine 25.2 (Scheme 25) in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, is converted to 28.1 as described in Scheme 7 for the preparation of the amine 7.10 from 7.9 and Scheme 9a for the preparation of 9a.4 from 7.10.

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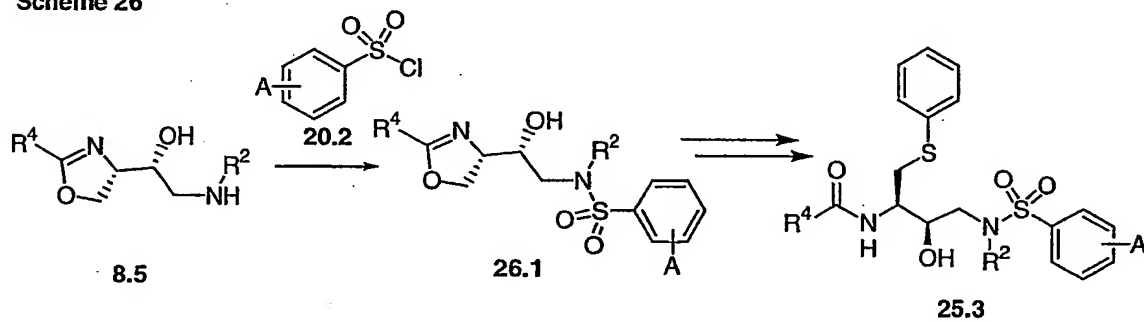
The reactions shown in Scheme 28 illustrate the preparation of the compounds sulfonamide 28.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 29 depicts the conversion of 28.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 4 in which X is sulfur. In this procedure 28.1 is converted, using the procedures described below, Schemes 47-99, into the compound 4.

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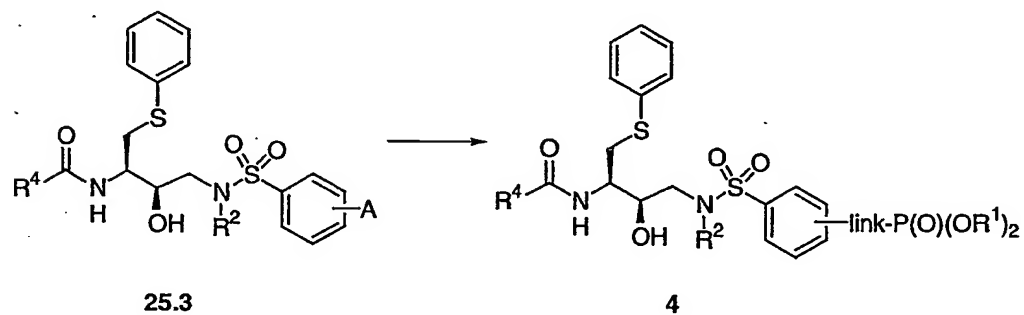
Scheme 25



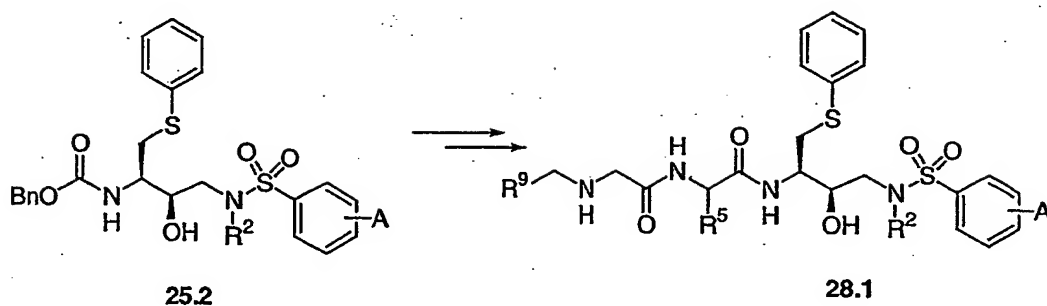
Scheme 26



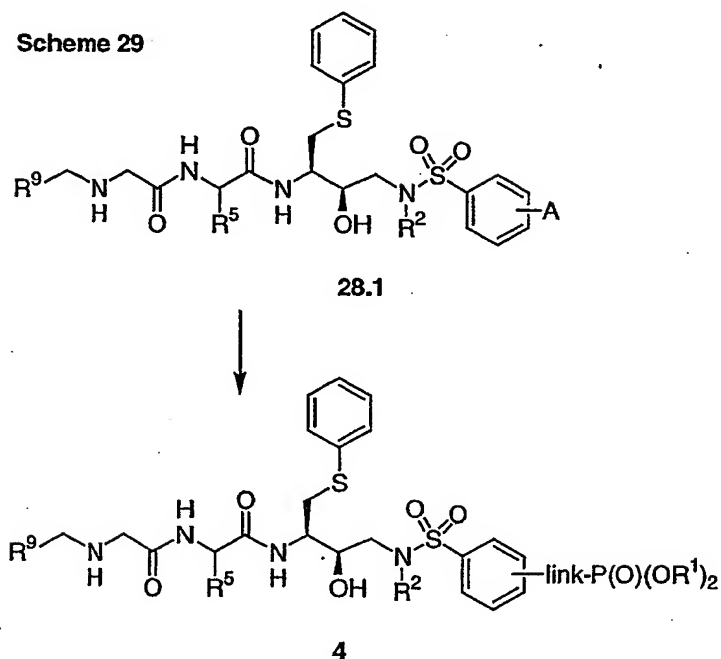
Scheme 27



Scheme 28



Scheme 29



Preparation of the phosphonate ester intermediates 5 in which X is a direct bond

- 5 Schemes 30 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the R group does not contain a primary or secondary amine group. As shown in Scheme 30, the amine 23.1 (Scheme 23) is reacted with the alcohol 30.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, to afford the carbamate 30.2. The reaction is performed under conditions described below, Scheme 98,
- 10 for making carbamates from amines and alcohols. The preparation of the 30.1 is described in

Schemes 83-86. The carbamate 30.2 is then deprotected using conditions described in Scheme 3 for removal of the benzyl groups to give 30.3. Treatment of 30.3 with the $R^4\text{COOH}$ acid 1.7 using the conditions described in Scheme 1 then afford the amide 30.4

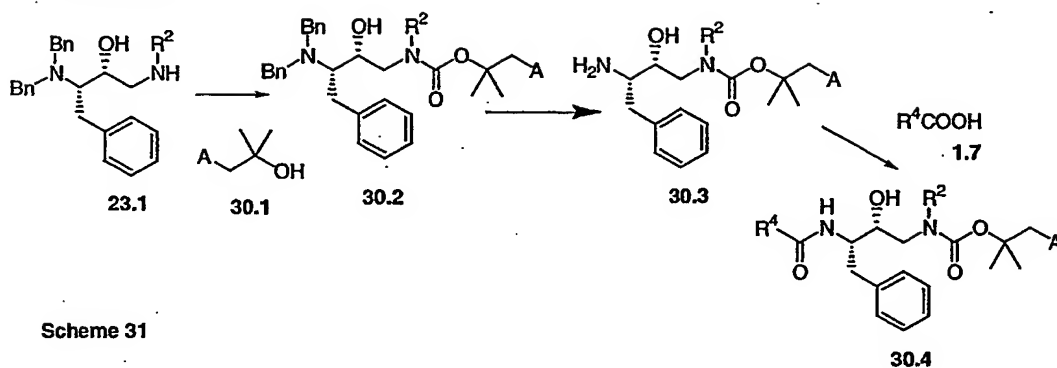
- 5 The reactions shown in Scheme 30 illustrate the preparation of the compound 30.4 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 31 depicts the conversion of this compounds 30.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 respectively, in which X is a direct bond. In this procedure, the amines 30.4 is converted, using the procedures described below, Schemes
- 10 47-99, into the compounds 5.

- Schemes 32 illustrates the preparation of the phosphonate esters 5 in which X is a direct bond and the $R_4\text{COOH}$ group contains an amine. The carbamate 30.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc, is
- 15 converted into the chloride 32.1 using conditions as described in Scheme 9a. Chloride 32.1 is then treated with amine 5.7 to give the amine 32.2, as described in Scheme 9a for the conversion of 7.10 into 9a.3.

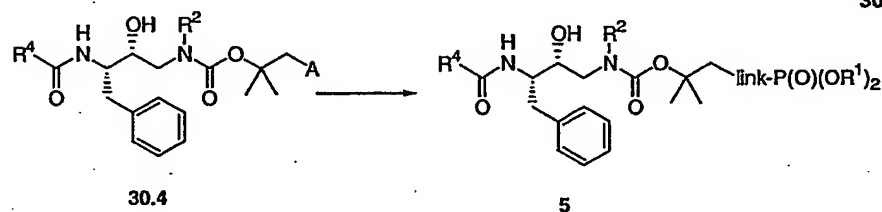
- The reactions shown in Scheme 32 illustrate the preparation of the compound 32.2 in which
- 20 the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 33 depicts the conversion of the compound 32.2 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 5 in which X is a direct bond. In this procedure, the compound 32.2 is converted, using the procedures described below, Schemes
- 47-99, into the compound 5.

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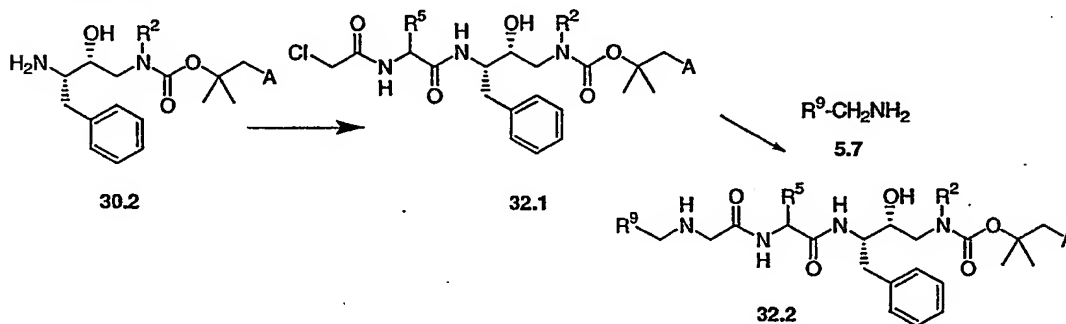
Scheme 30



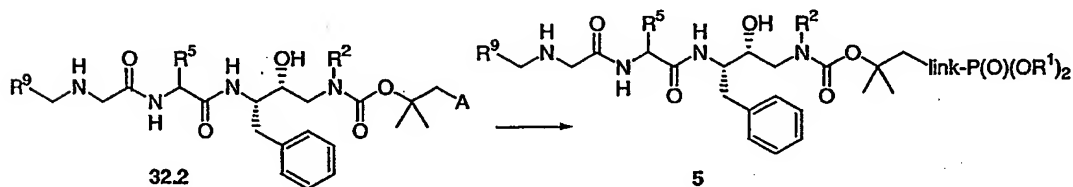
Scheme 31



Scheme 32



Scheme 33



Preparation of the phosphonate ester intermediates 5 in which X is a sulfur

- 5 The intermediate phosphonate ester **5**, in which the group A is attached to a sulfur linked aryl moiety, is prepared as shown in Schemes 34-36. Amine **25.1** prepared according to Scheme 25, is treated with alcohol **30.1** in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, using the conditions described below ,

Scheme 98, to give the carbamate 34.1. The carbamate 34.1 is then converted as described in Scheme 7, for the conversion of 7.9 to 7.11, to the product 34.2. Alternatively the amine 8.5 prepared according to Scheme 8 can be reacted with alcohol 30.1 under conditions described in Scheme 98 to give the carbamate 35.1. Further modification according to the conditions
5 described in Scheme 8, except incorporating thiophenol, then affords sulfonamide 34.2.

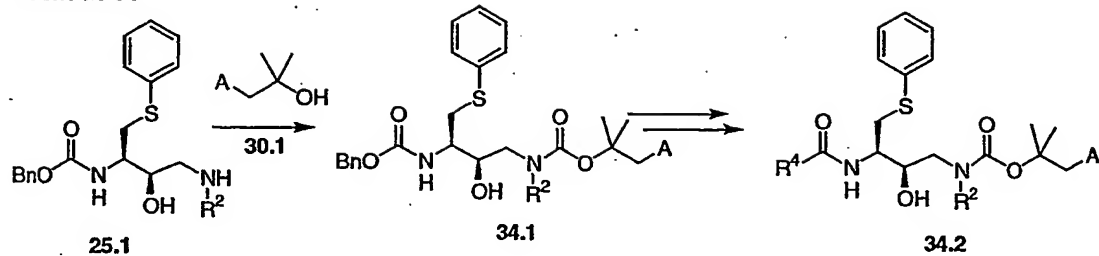
The reactions shown in Scheme 34-35 illustrate the preparation of the compounds sulfonamide 34.2 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 36 depicts the conversion of 34.2 in which A is [OH],
10 [SH], [NH], Br etc, into the phosphonate 5 in which X is sulfur. In this procedure 34.2 is converted, using the procedures described below, Schemes 47-99, into the compound 5.

Preparation of the intermediate phosphonate ester 5, in which the group A is attached to a sulfur linked aryl moiety, and the R₄COOH group contains an amine are prepared as shown in
15 Schemes 37-38. Carbamate 34.1 (Scheme 35) in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, is converted to 37.1, as described in Scheme 7 for the preparation of the amine 7.10 from 7.9 and Scheme 9a for the preparation of 9a.4 from 7.10..

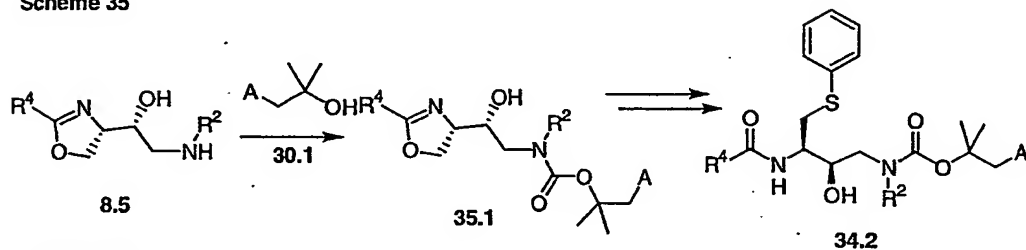
20 The reactions shown in Scheme 37 illustrate the preparation of the compounds sulfonamide 37.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 38 depicts the conversion of 37.1 in which A is [OH], [SH], [NH], Br etc, into the phosphonate 5 in which X is sulfur. In this procedure 37.1 is converted, using the procedures described below, Schemes 47-99, into the compound 5.

25

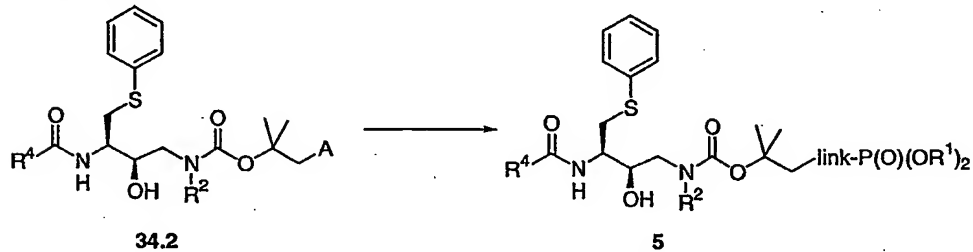
Scheme 34



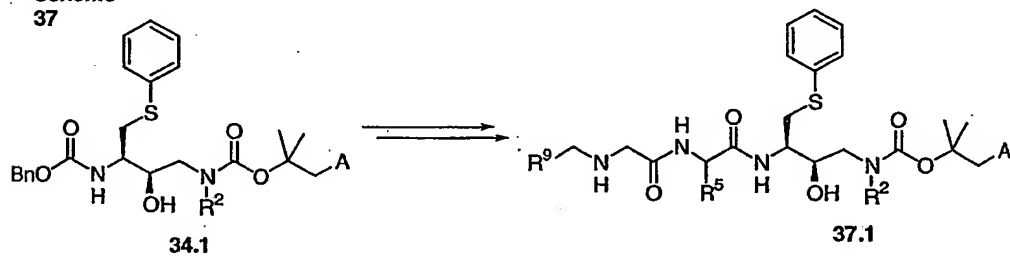
Scheme 35



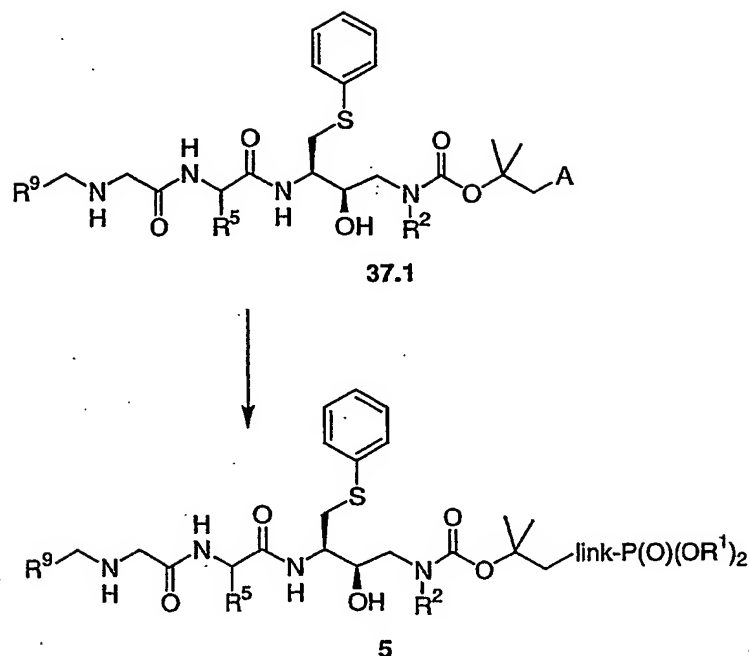
Scheme 36



Scheme 37



Scheme 38

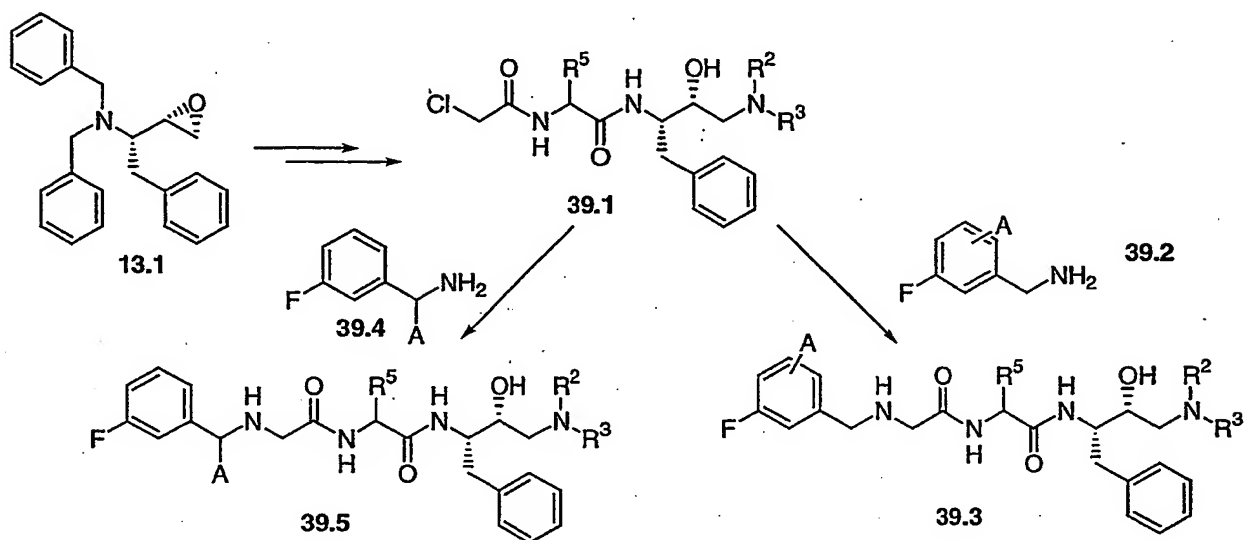


Preparation of the phosphonate ester intermediates 6 and 7 in which X is a direct bond

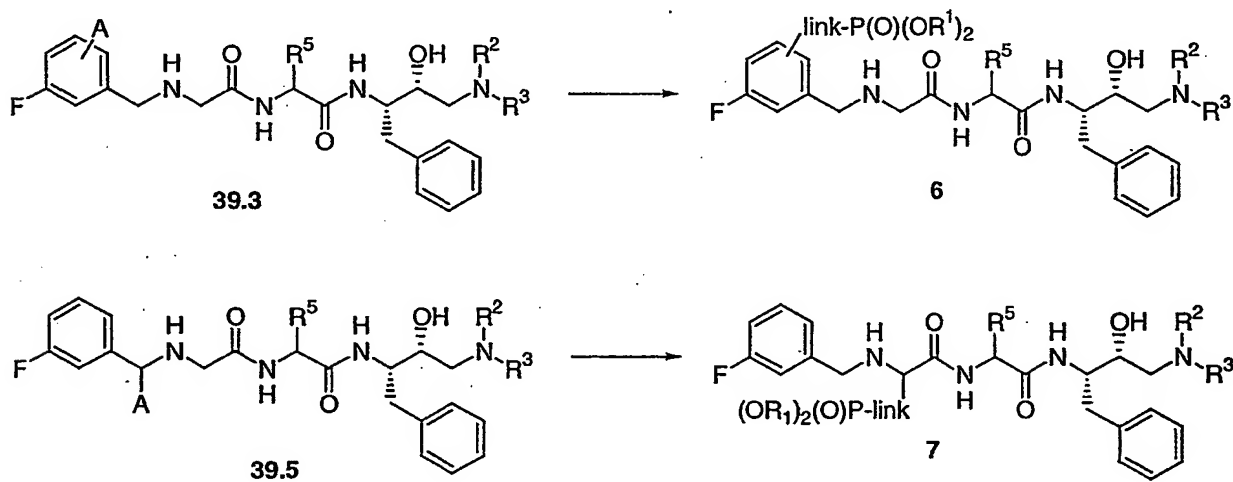
- 5 Schemes 39-40 illustrate the preparation of the phosphonate esters 6 and 7 in which X is a direct bond. As shown in Scheme 39, the epoxide 13.1, prepared as described in Scheme 13 is converted to the chloride 39.1, as described in Scheme 3, for the preparation of 3.4, and Scheme 5, for the conversion of 3.4 into 5.6. The chloride 39.1 is then reacted with the amine 39.2 or 39.4, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor
- 10 such as [OH], [SH], [NH], Br etc, to afford the amine 39.3 and 39.5 respectively. The reaction is performed under the same conditions as described above, Scheme 5 for the preparation of the amine 5.8 from 5.6. The preparation of 39.2 and 39.4, amines in which A is link-P(O)(OR¹)₂, are shown in Schemes 79-80 and Schemes 81-82 respectively.
- 15 The reactions shown in Scheme 39 illustrate the preparation of the compounds 39.3 and 39.5 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 40 depicts the conversion of these compounds 39.3 and 39.5 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 6 and 7 respectively, in

which X is a direct bond. In this procedure, the amines 39.3 and 39.5 are converted, using the procedures described below, Schemes 47-99, into the compounds 6 and 7 respectively.

Scheme 39



Scheme 40



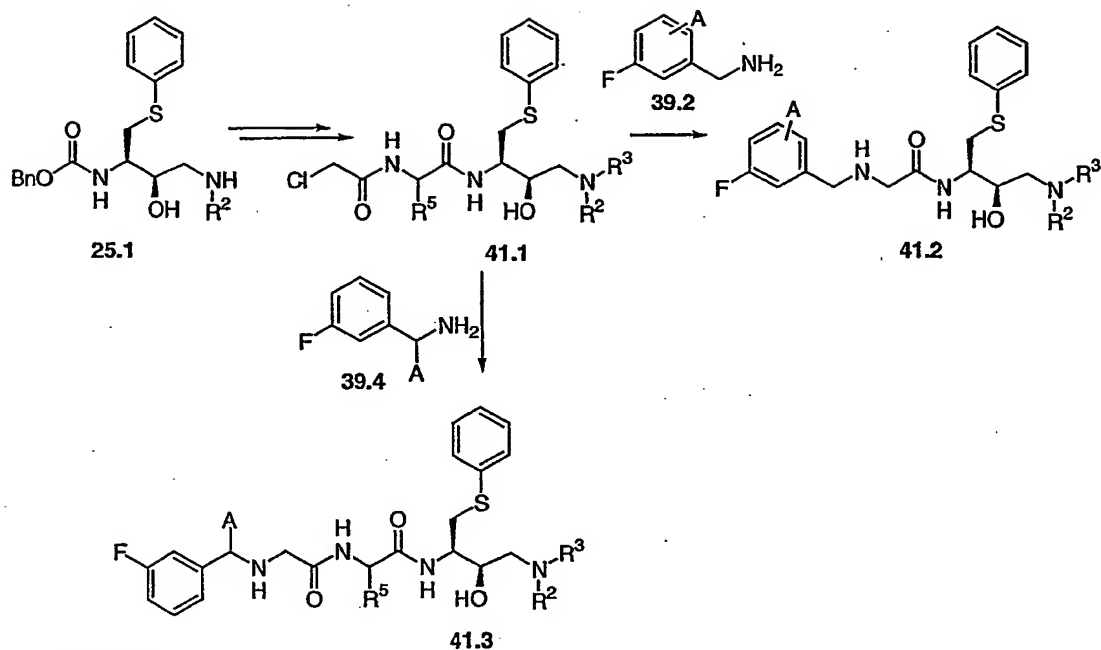
Preparation of the phosphonate ester intermediates 6 and 7 in which X is a sulfur

The intermediate phosphonate esters 6 and 7, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Scheme 41-42. The amine 25.1 (Scheme 25) is

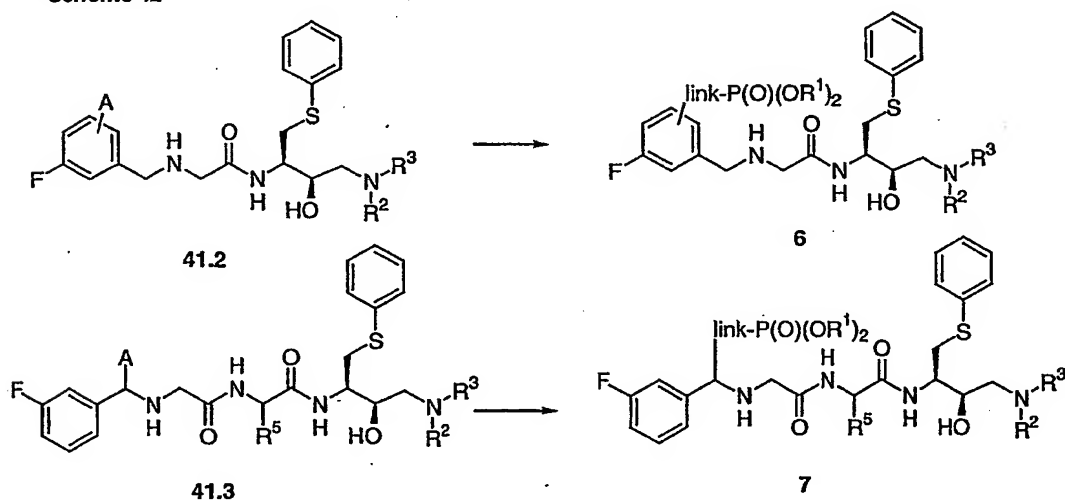
converted to the chloride **41.1** as described in Scheme 7 for the preparation of **7.10** from **7.8**, and Scheme 9a for conversion of **7.10** to **9a3**. The chloride **41.1** is then treated with amine **39.2** or amine **39.4**, in which substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 5, to give the amines **41.2** and **41.3** respectively.

The reactions shown in Scheme 41 illustrate the preparation of the compounds **41.2** and **41.3** in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 42 depicts the conversion of **41.2** and **41.3** in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester **6** and **7** in which X is sulfur. In this procedure **41.2** or **41.3** is converted, using the procedures described below, Schemes 47-99, into the compound **6** and **7**.

Scheme 41



Scheme 42



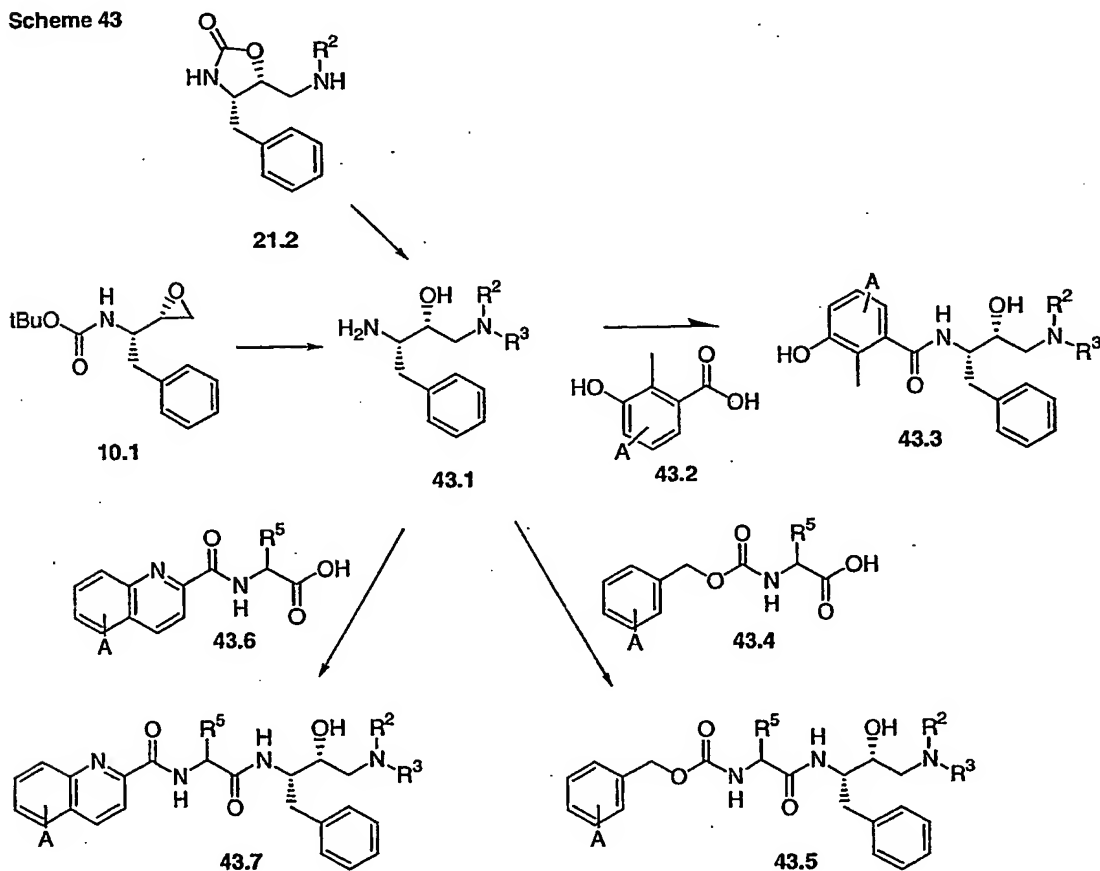
Preparation of the phosphonate ester intermediates 8-10 in which X is a direct bond

- 5 Schemes 43-44 illustrate the preparation of the phosphonate esters 8-10 in which X is a direct bond. As shown in Scheme 43, the amine 43.1 prepared from 10.1 or 21.2 is reacted with the acid 43.2, 43.4 or 43.6, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$ or a precursor such as [OH], [SH], [NH], Br etc, to afford the amide 43.3, 43.5 and 43.7 respectively. The reaction is performed under the same conditions as described above, Scheme

1 for the preparation of the amide 1.8. Amine 43.1 is prepared from epoxide 10.1 using the conditions described in Scheme 1 except utilising 10.1 in place of 1.1. Amine 43.1 is prepared from 21.2 according to the conditions described in Scheme 2 except utilizing 21.2 in place of 2.1. The preparation of the acid 43.2 is described in Schemes 47-51, acid 43.4 is described in
 5 Schemes 87-91, and acid 43.6 is described in Schemes 52-55.

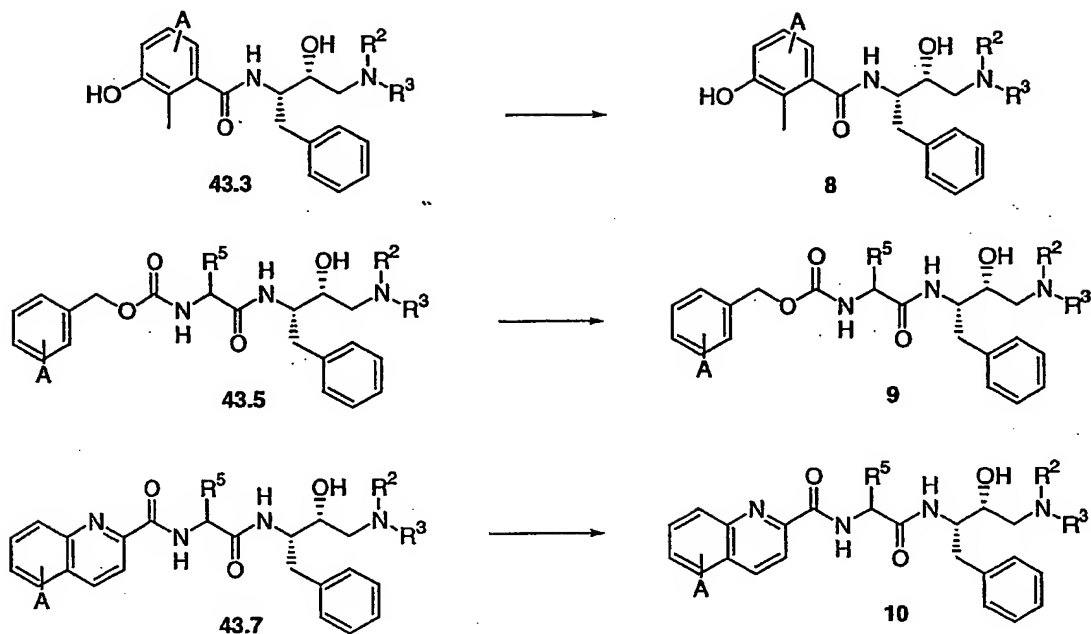
The reactions shown in Scheme 43 illustrate the preparation of the compounds 43.3, 43.5 and 43.7 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 44 depicts the conversion of these compounds 43.3, 43.5,
 10 and 43.7 in which A is [OH], [SH], [NH], Br etc, into the phosphonate esters 8, 9 and 10 respectively, in which X is a direct bond. In this procedure, the amines 43.3, 43.5 and 43.7 are converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9, and 10 respectively.

Scheme 43



15

Scheme 44



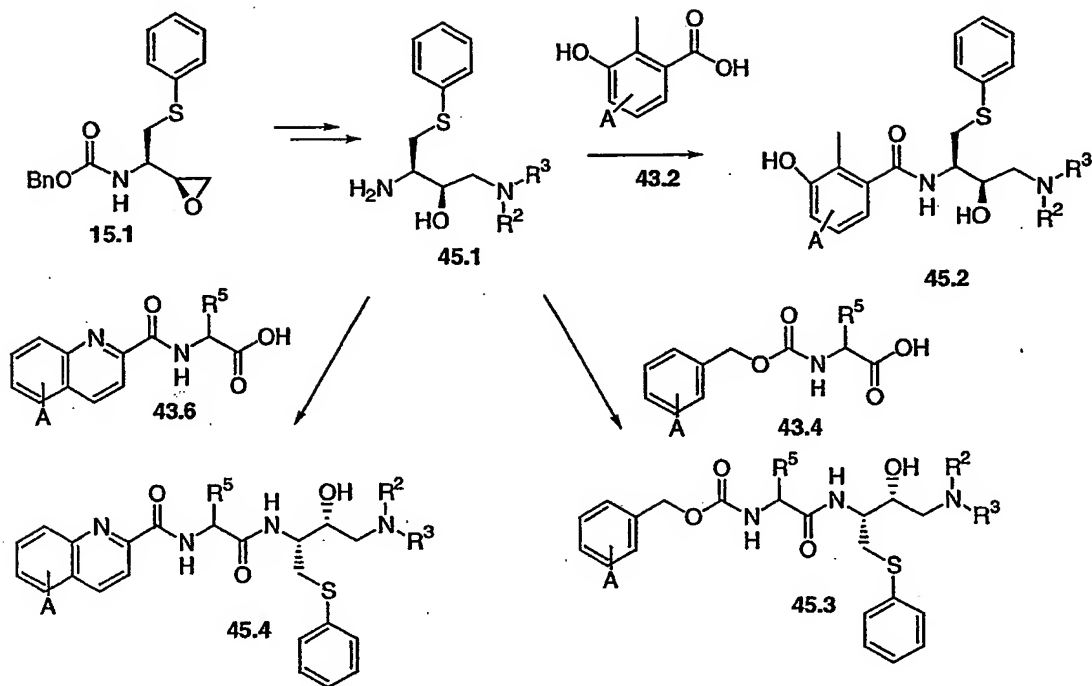
Preparation of the phosphonate ester intermediates 8-10 in which X is a sulfur

- 5 The intermediate phosphonate esters 8-10, in which the group A is attached to a sulfur linked aryl moiety, are prepared as shown in Schemes 45-46. In Scheme 45, epoxide 15.1 is prepared from mesylate 7.1 using the conditions described in Scheme 7 except incorporating thiophenol for thiol 7.2. The epoxide 15.1 is then converted to amine 45.1 according to the conditions described in Scheme 7 for the preparation of 7.10 from 7.7. Amine 45.1 is then
- 10 treated with acids 43.2, 43.4 or 43.6, in which substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc, as described in Scheme 7, to give the amides 45.2, 45.3, and 45.4 respectively.

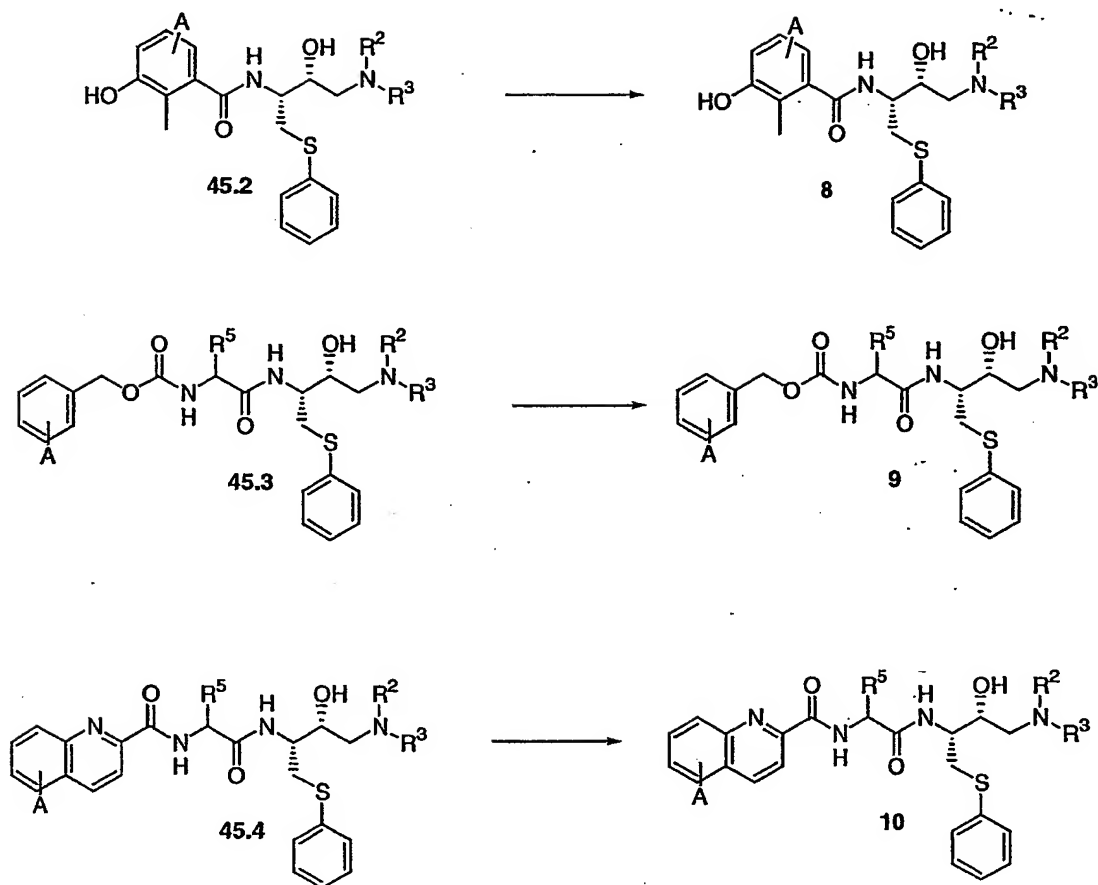
The reactions shown in Scheme 45 illustrate the preparation of the compounds 45.2, 45.3, and

15 45.4 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor such as [OH], [SH], [NH], Br etc. Scheme 46 depicts the conversion 45.2, 45.3, and 45.4 in which A is [OH], [SH], [NH], Br etc, into the phosphonate ester 8, 9 and 10 respectively in which X is sulfur. In this procedure 45.2, 45.3, and 45.4 is converted, using the procedures described below, Schemes 47-99, into the compounds 8, 9 and 10 respectively.

Scheme 45



Scheme 46



Preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2.

- 5 Schemes 47 - 51 illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids 43.2 which are employed in the preparation of the phosphonate esters 8.

Scheme 47 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 47.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 47.2. This compound is reacted with a chlorodialkyl phosphite 47.3 to yield the phenylphosphonate ester 47.4, which upon deprotection affords the carboxylic acid 47.5.

10

- For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, **47.6**, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane **47.7**, as described in
- 5 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester **47.8**. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester **47.9**, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether **47.10**. Halogen-metal exchange is performed by the
- 10 reaction of the substrate **47.10** with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite **47.3**, to produce the phosphonate **47.11**. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid **47.12**.
- 15 Using the above procedures, but employing, in place of the bromo compound **47.6**, different bromo compounds **47.1**, there are obtained the corresponding products **47.5**.

- Scheme 48 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.
- 20 In this method, a suitably protected dimethyl hydroxybenzoic acid, **48.1**, is reacted with a brominating agent, so as to effect benzylic bromination. The product **48.2** is reacted with a sodium dialkyl phosphite, **48.3**, as described in J. Med. Chem., 1992, 35, 1371, to effect displacement of the benzylic bromide to afford the phosphonate **48.4**. Deprotection of the carboxyl function then yields the carboxylic acid **48.5**.
- 25 For example, 2,5-dimethyl-3-hydroxybenzoic acid, **48.6**, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester **48.7**. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or
- 30 diisopropylethylamine. The product **48.7** is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford the bromomethyl product **48.8**. This compound is then reacted with a sodium dialkyl

phosphite 48.3 in tetrahydrofuran, as described above, to afford the phosphonate 48.9.
Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as
described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid 48.10.
Using the above procedures, but employing, in place of the methyl compound 48.6, different
5 methyl compounds 48.1, there are obtained the corresponding products 48.5.

Scheme 49 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids
in which the phosphonate group is attached by means of an oxygen or sulfur atom.
In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic
10 acid 49.1 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl
hydroxymethyl phosphonate 49.2, to afford the coupled product 49.3, which upon
deprotection affords the carboxylic acid 49.4.
For example, 3,6-dihydroxy-2-methylbenzoic acid, 49.5, the preparation of which is described
in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 49.6, by
15 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis,
by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with
one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as
described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley,
Second Edition 1990, p 77, to afford the mono-silyl ether 49.7. This compound is then reacted
20 with a dialkyl hydroxymethylphosphonate 49.2, under the conditions of the Mitsunobu
reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described,
for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.
448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum,
2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in
25 an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl
azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The
procedure is also described in Org. React., 1992, 42, 335-656. The reaction affords the
coupled product 49.8. Deprotection, for example by treatment with trifluoroacetic acid at
ambient temperature, as described in J. Chem. Soc., C, 1191, 1966, then affords the phenolic
30 carboxylic acid 49.9.

Using the above procedures, but employing, in place of the phenol 49.5, different phenols or
thiophenols 49.1, there are obtained the corresponding products 49.4.

Scheme 50 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains.

In this method, a dialkyl alkenylphosphonate 50.2 is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid 50.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product 50.3 is deprotected to afford the phosphonate 50.4; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid 50.5.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid 50.6, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester 50.7 as described above. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate 50.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, using the conditions described above to afford the product 50.9. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products 50.10 and 50.11.

Using the above procedures, but employing, in place of the bromo compound 50.6, different bromo compounds 50.1, and/or different phosphonates 50.2, there are obtained the corresponding products 50.4 and 50.5.

Scheme 51 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.

In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 51.1 is converted to the corresponding boronic acid 51.2, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 51.3. The product 51.4 is then deprotected to afford the diaryl phosphonate product 51.5.

For example, the silylated OBO ester **51.6**, prepared as described above, (Scheme 47), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp.

Radiopharm., 1992, 31, 175, is converted into the boronic acid **51.7**, as described above. This material is coupled with a dialkyl 4-bromophenyl phosphonate **51.8**, prepared as described in

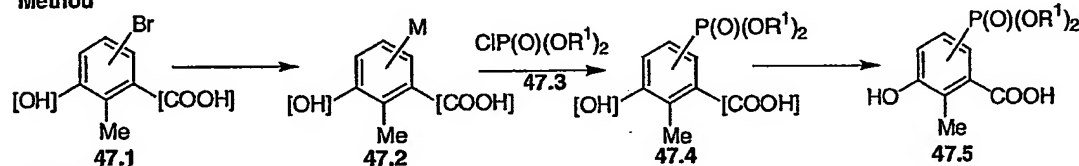
5 J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate **51.9**.

Deprotection, as described above, then affords the benzoic acid **51.10**.

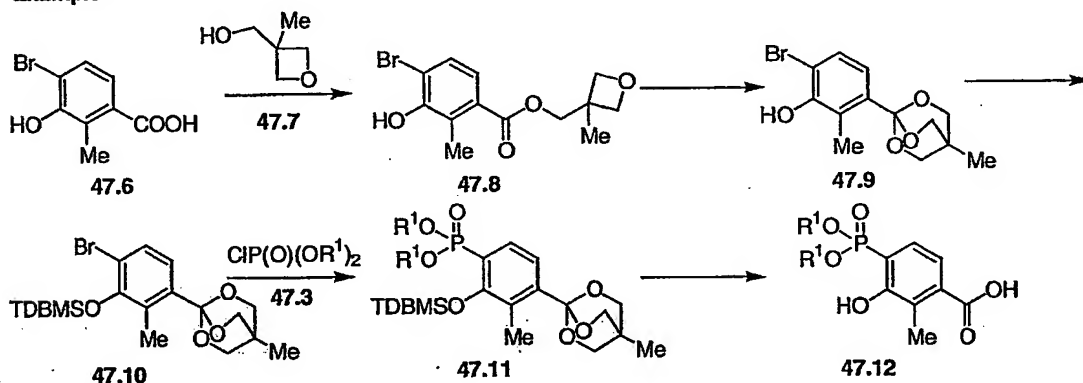
Using the above procedures, but employing, in place of the bromo compound **51.6**, different
10 bromo compounds **51.1**, and/or different phosphonates **51.3**, there are obtained the corresponding carboxylic acid products **51.5**.

Scheme 47

Method

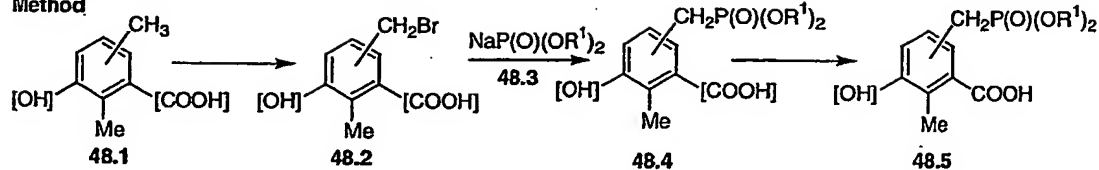


Example

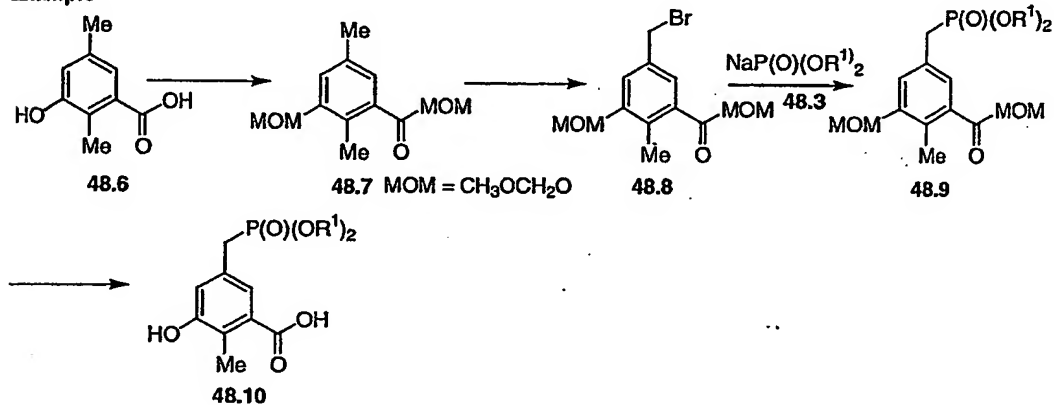


Scheme 48

Method

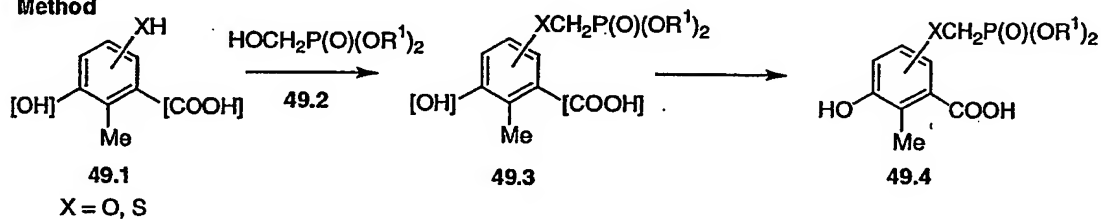


Example

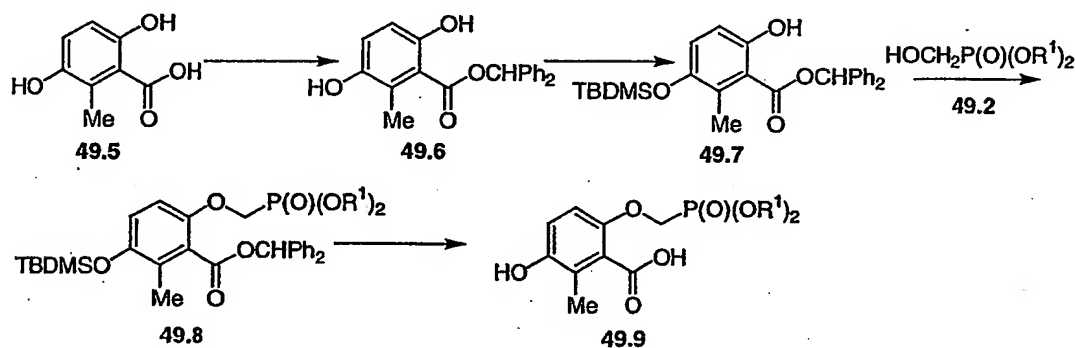


Scheme 49

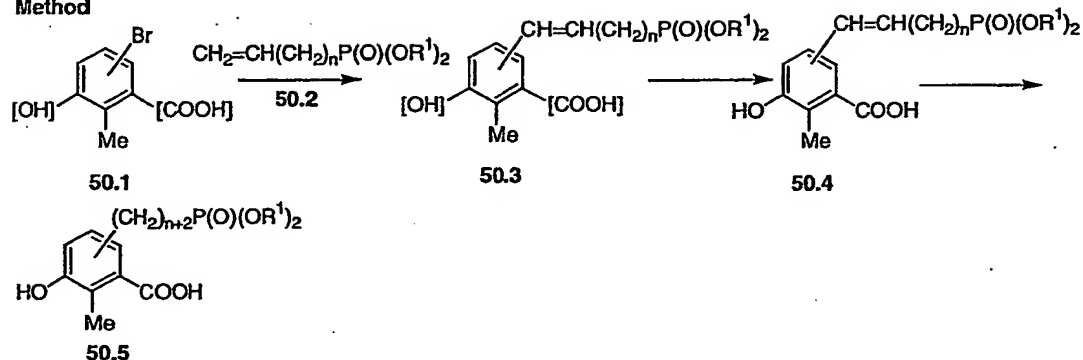
Method



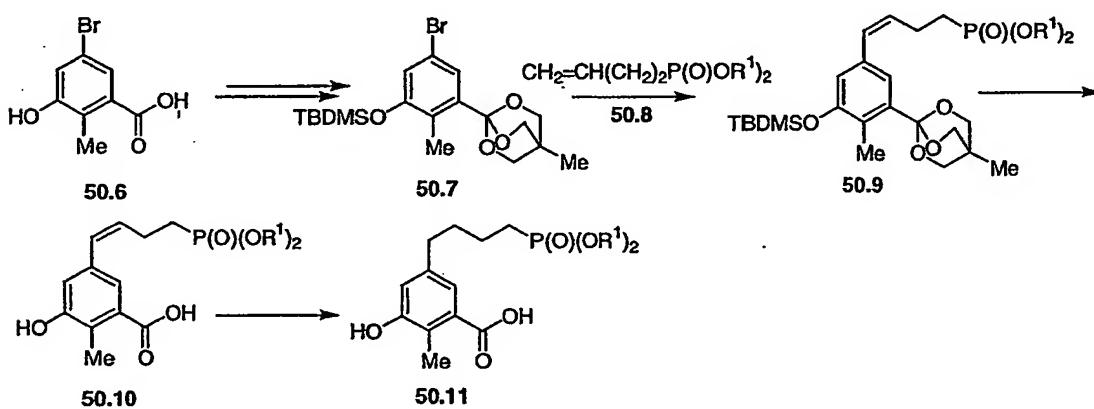
Example



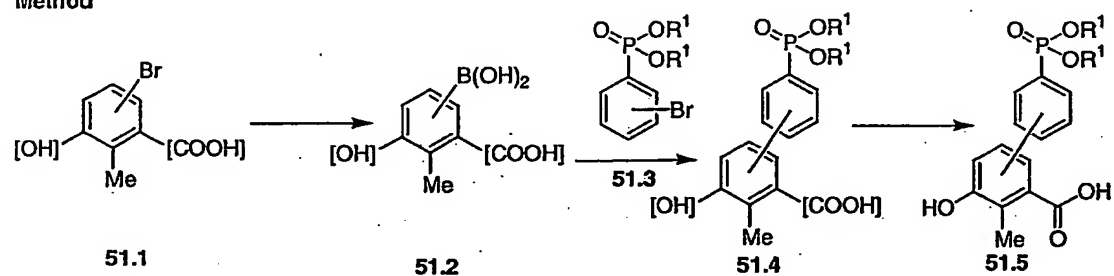
Scheme 50
Method



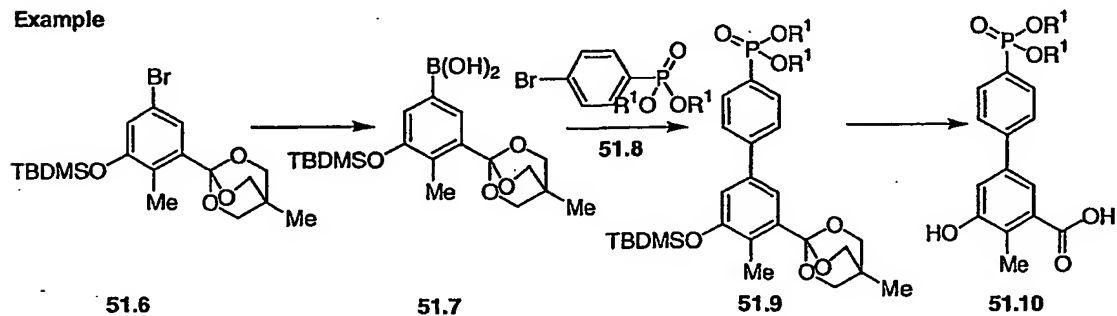
Example



Scheme 51
Method



Example



Preparation of quinoline 2-carboxylic acids 43.6 incorporating phosphonate moieties.

The reaction sequences depicted in Schemes 43 - 46 for the preparation of the phosphonate esters 10 employ a quinoline-2-carboxylic acid reactant 43.6 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$ or a precursor thereto, such as [OH], [SH] Br etc. A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het. Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described, for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.

Scheme 52 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 52.1 is reacted with an alkyl pyruvate ester 52.2, in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester 52.3. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid 52.4. The carboxylic acid product 52.4 in which X is NH_2 can be further transformed into the corresponding compounds 52.6 in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic

Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol 52.6, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, 52.6, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol 52.6, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters 52.3 instead of the carboxylic acids 52.5.

- For example, 2,4-diaminobenzaldehyde 52.7 (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate 52.2 in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate 52.8. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 52.9. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate 52.10 by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, 52.11, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid 52.11, Z = Br. Alternatively, the diazonium tetrafluoroborate 52.10 is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid 52.11, Z = SH.

- Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 52.7, different aminobenzaldehydes 52.1, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids 52.6 are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes 53 – 55) into phosphonate-containing derivatives.

- Scheme 53 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester 53.1 is transformed, via a diazotization procedure as described above (Scheme 52) into the corresponding phenol or

thiol 53.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 53.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 53.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products 53.4. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 53.5. The product is then coupled with a suitably protected aminoacid derivative 53.6 to afford the amide 53.7. The reaction is performed under similar conditions to those described above, Scheme 1. The ester protecting group is then removed to yield the carboxylic acid 53.8.

For example, methyl 6-amino-2-quinoline carboxylate 53.9, prepared as described in *J. Het. Chem.*, 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate 53.10. This material is reacted with a dialkyl hydroxymethylphosphonate 53.11 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 53.12. Basic hydrolysis then afford the carboxylic acid 53.13. The latter compound is then converted, as described above, into the aminoacid derivative 53.16.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate 53.9, different aminoquinoline carboxylic esters 53.1, and/or different dialkyl hydroxymethylphosphonates 53.3 the corresponding phosphonate ester products 53.8 are obtained.

Scheme 54 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 54.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 54.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as

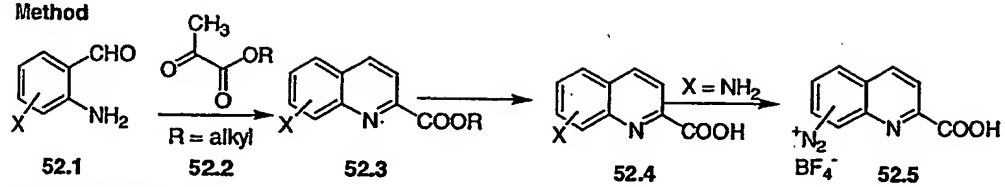
dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound 54.1 and the olefin 54.2 affords the olefinic ester 54.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 54.4. The latter compound is then transformed, as described above, into the homolog 54.5. Optionally, the unsaturated carboxylic acid 54.4 can be reduced to afford the saturated analog 54.6. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product 54.6 is then converted, as described above (Scheme 53) into the aminoacid derivative 54.7.

For example, methyl 7-bromoquinoline-2-carboxylate, 54.8, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate 54.9 (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 54.10. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 54.11. The latter compound is reacted with diimide, prepared by basic hydrolysis of diethyl azodicarboxylate, as described in Angew. Chem. Int. Ed., 4, 271, 1965, to yield the saturated product 54.12. The latter compound is then converted, as described above, into the aminoacid derivative 54.13. The unsaturated product 54.11 is similarly converted into the analog 54.14.

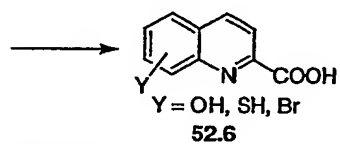
Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate 54.8, different bromoquinoline carboxylic esters 54.1, and/or different dialkyl alkenylphosphonates 54.2, the corresponding phosphonate ester products 54.5 and 54.7 are obtained.

Scheme 52

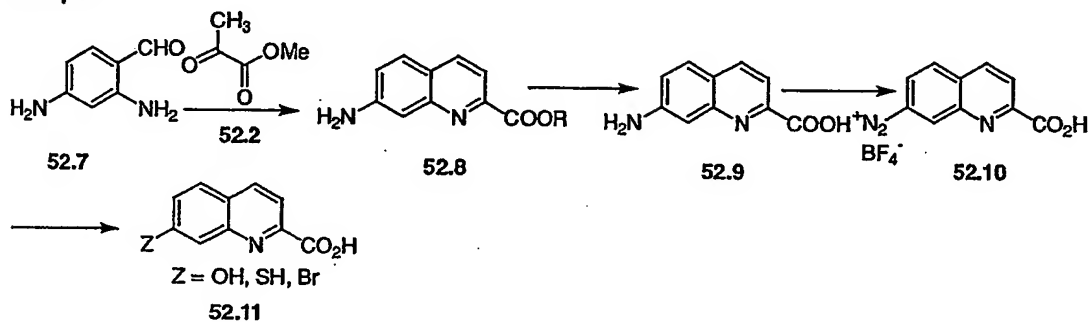
Method



$\text{X} = \text{OH}, \text{SH}, \text{NH}_2, \text{Br}$

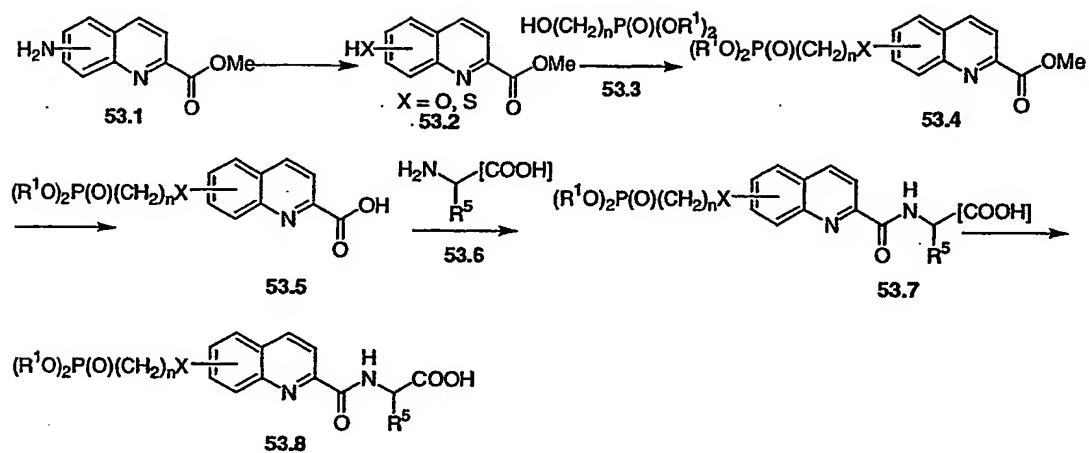


Example

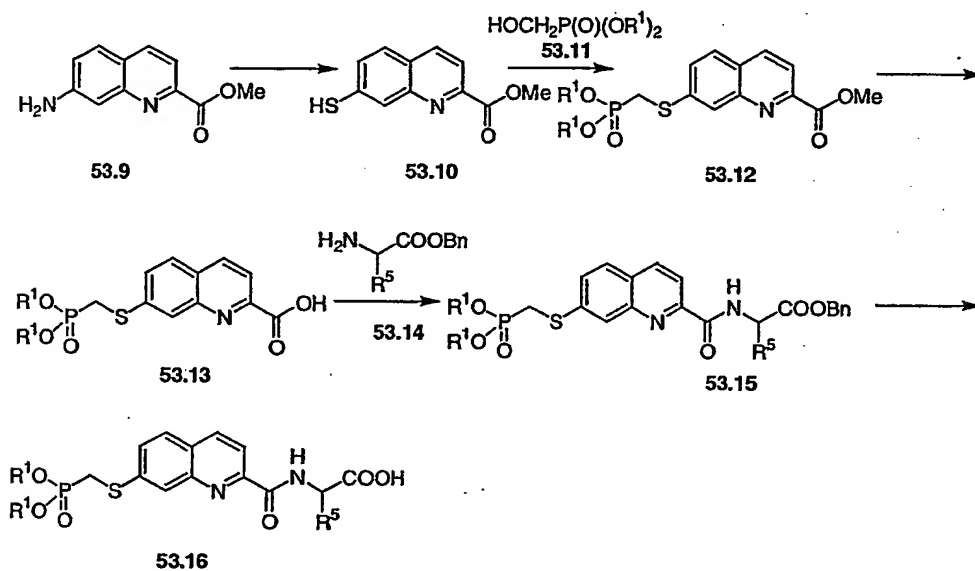


Scheme 53

Method

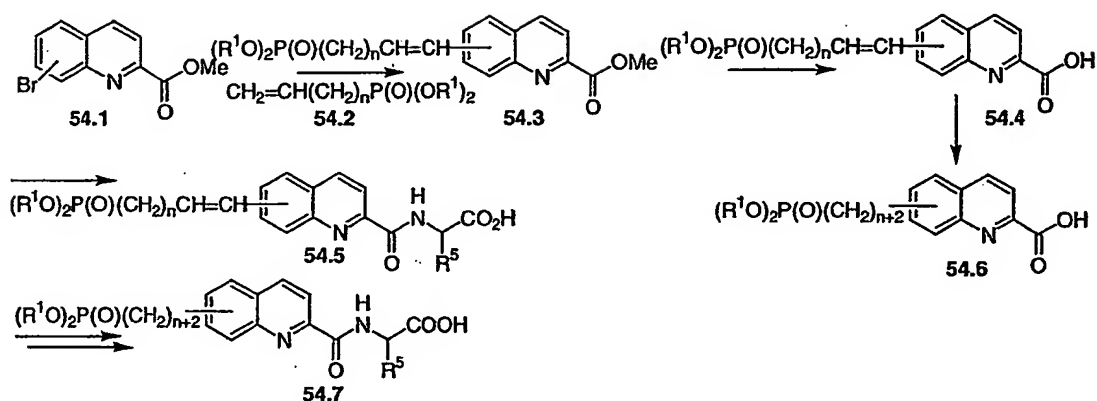


Example

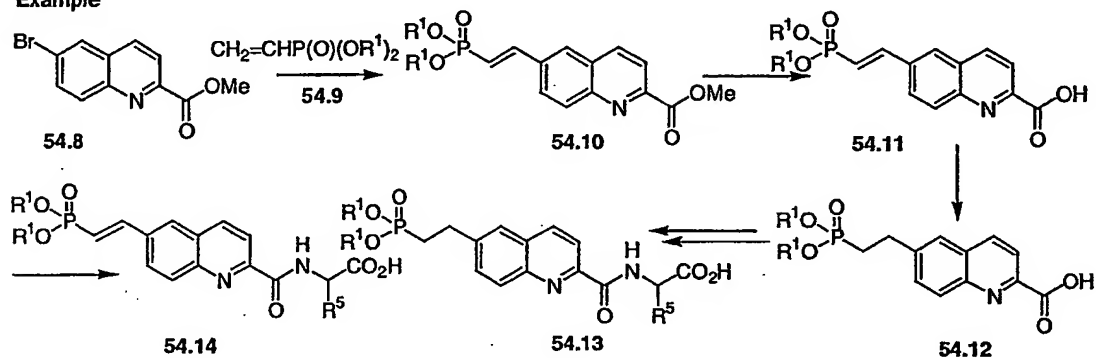


Scheme 54

Method



Example

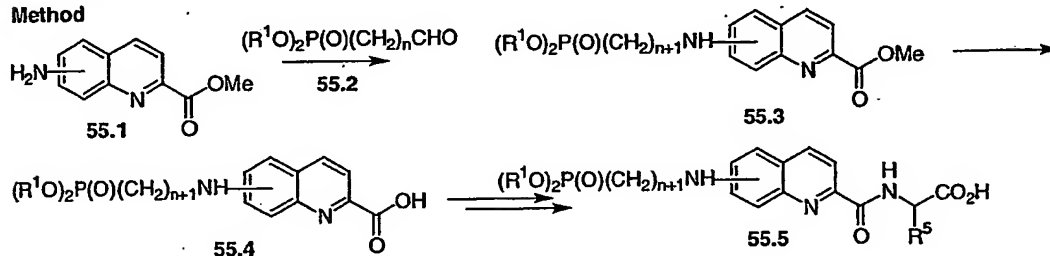


Scheme 55 depicts the preparation of quinoline-2-carboxylic acid derivatives 55.5 in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate 55.1 is reacted with a phosphonate aldehyde 55.2 under reductive amination conditions, to afford the aminoalkyl product 55.3. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p 421, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in J. Org. Chem., 55, 2552, 1990. The ester product 55.3 is then hydrolyzed to yield the free carboxylic acid 55.4. The latter compound is then converted, as described above, into the aminoacid derivative 55.5.

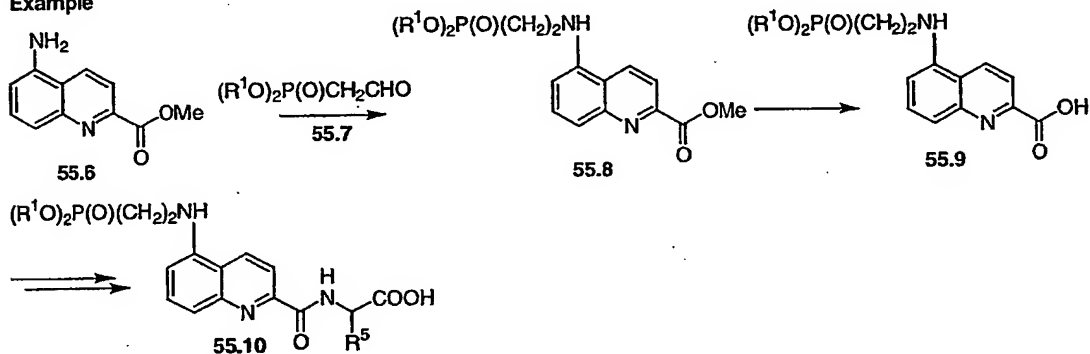
For example, methyl 7-aminoquinoline-2-carboxylate **55.6**, prepared as described in J. Am. Chem. Soc., 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **55.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **55.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **55.9**. The latter compound is then converted, as described above, into the aminoacid derivative **55.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **55.7**, different formylalkyl phosphonates **55.2**, and/or different aminoquinolines **55.1**, the corresponding products **55.5** are obtained.

Scheme 55

Method



Example



10

Preparation of phenylalanine derivatives 1.1 incorporating phosphonate moieties.

Scheme 56 illustrates the conversion of variously substituted phenylalanine derivatives **56.1** into epoxides **1.1**, the incorporation of which into the compounds **1** is depicted in Schemes **1** and **3**.

A number of compounds **56.1** or **56.2**, for example those in which X is 2, 3, or 4-OH, or X is 4-NH₂ are commercially available. The preparations of different compounds **56.1** or **56.2** are described in the literature. For example, the preparation of compounds **56.1** or **56.2** in which

X is 3-SH, 4-SH, 3-NH₂, 3-CH₂OH or 4-CH₂OH, are described respectively in WO0036136, J. Am. Chem. Soc., 1997, 119, 7173, Helv. Chim. Acta, 1978, 58, 1465, Acta Chem. Scand., 1977, B31, 109 and Syn. Com., 1998, 28, 4279. Resolution of compounds 56.1, if required, can be accomplished by conventional methods, for example as described in Recent Dev. Synth. Org. Chem., 1992, 2, 35.

The variously substituted aminoacids 56.2 are protected, for example by conversion to the BOC derivative 56.3, by treatment with BOC anhydride, as described in J. Med. Chem., 1998, 41, 1034. The product 56.3 is then converted into the methyl ester 56.4, for example by treatment with ethereal diazomethane. The substituent X in 56.4 is then transformed, using the methods described below, Schemes 57-59, into the group A. The products 56.5 are then converted, via the intermediates 56.6 - 56.9, into the epoxides 1.1. The methyl ester 56.5 is first hydrolyzed, for example by treatment with one molar equivalent of aqueous methanolic lithium hydroxide, or by enzymatic hydrolysis, using, for example, porcine liver esterase, to afford the carboxylic acid 56.6. The conversion of the carboxylic acid 56.6 into the epoxide 1.1, for example using the sequence of reactions which is described in J. Med. Chem., 1994, 37, 1758, is then effected. The carboxylic acid is first converted into the acid chloride, for example by treatment with oxalyl chloride, or into a mixed anhydride, for example by treatment with isobutyl chloroformate, and the activated derivative thus obtained is reacted with ethereal diazomethane, to afford the diazoketone 56.7. The diazoketone is converted into the chloroketone 56.8 by reaction with anhydrous hydrogen chloride, in a suitable solvent such as diethyl ether. The latter compound is then reduced, for example by the use of sodium borohydride, to produce a mixture of chlorohydrins from which the desired 2S, 3S diastereomer 56.9 is separated by chromatography. This material is reacted with ethanolic potassium hydroxide at ambient temperature to afford the epoxide 1.1. Optionally, the above described series of reactions can be performed on the methyl ester 56.4, so as to yield the epoxide 1.1 in which A is OH, SH, NH, Nalkyl or CH₂OH.

Methods for the transformation of the compounds 56.4, in which X is a precursor group to the substituent link-P(O)(OR¹)₂, are illustrated in Schemes 57-59.

Scheme 56a illustrates the conversion of variously substituted phenylalanine derivatives 56a.1 into epoxides 3.1, the incorporation of which into the compounds 1 is depicted in Schemes 3. Starting from the same reagents described above, Scheme 56, the compound 56.2 is converted

into the epoxide **56a.6** as described in J. Org. Chem 1996,61, 3635. The amino acid **56.2** is converted to the tribenzyl ester **56a.3** by treatment with benzyl bromide in ethanol in the presence of potassium carbonate. The substituent X in **56a.3** is then transformed, using the methods described below, Schemes 57-59, into the group A, compound **56a.4**. These methods describe procedures in which the amine is BOC protected. However the same procedures are applicable to other amine protecting groups such as dibenzyl. The products **56a.4** are then converted, via the intermediates **56a.5** into the epoxides **3.1**. The ester **56a.4** is reduced with lithium aluminum hydride to the alcohol which is then oxidized to the aldehyde **56a.4** by treatment with pyridine sulfur trioxide in DMSO and triethylamine. The aldehyde **56a.4** is then converted to the epoxide **3.1** by treatment with chloromethylbromide and excess lithium in THF at -65 °C. A mixture of isomers are produced which are separated by chromatography.

Scheme 57 depicts the preparation of epoxides **57.4** incorporating a phosphonate group linked to the phenyl ring by means of a heteroatom O, S or N. In this procedure, the phenol, thiol, amine or carbinol **57.1** is reacted with a derivative of a dialkyl hydroxymethyl phosphonate **57.2**. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is OH, SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is CH₂OH, a base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester **57.3**, which, employing the sequence of reactions shown in Scheme 56 or 56a, is transformed into the epoxide **57.4**.

For example, 2-tert.-butoxycarbonylamino-3-(4-hydroxy-phenyl)-propionic acid methyl ester, **57.5** (Fluka) is reacted with a dialkyl trifluoromethanesulfonyloxy phosphonate **57.6**, prepared as described in Tet. Lett., 1986, 27, 1477, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the ether product **57.5**. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide **57.8**. Using the above procedures, but employing different phenols, thiols, amines and carbinols **57.1** in place of **57.5**, and/or different phosphonates **57.2**, the corresponding products **57.4** are obtained.

Scheme 58 illustrates the preparation of a phosphonate moiety is attached to the phenylalanine scaffold by means of a heteroatom and a multi-carbon chain.

In this procedure, a substituted phenylalanine derivative 58.1 is reacted with a dialkyl bromoalkyl phosphonate 58.2 to afford the product 58.3. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a suitable base such as sodium hydride or cesium carbonate. The product is then transformed, using the sequence of reactions shown in Scheme 56, into the epoxide 58.4.

For example, the protected aminoacid 58.5, prepared as described above (Scheme 56) from 3-mercaptophenylalanine, the preparation of which is described in WO 0036136, is reacted with a dialkyl 2-bromoethyl phosphonate 58.6, prepared as described in Synthesis, 1994, 9, 909, in the presence of cesium carbonate, in dimethylformamide at ca 60°, to afford the thioether product 58.7. The latter compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide 58.8.

Using the above procedures, but employing different phenols, thiols, and amines 58.1 in place of 58.5, and/or different phosphonates 58.2, the corresponding products 58.4 are obtained.

Scheme 59 depicts the preparation of phosphonate-substituted phenylalanine derivatives in which the phosphonate moiety is attached by means of an alkylene chain incorporating a heteroatom.

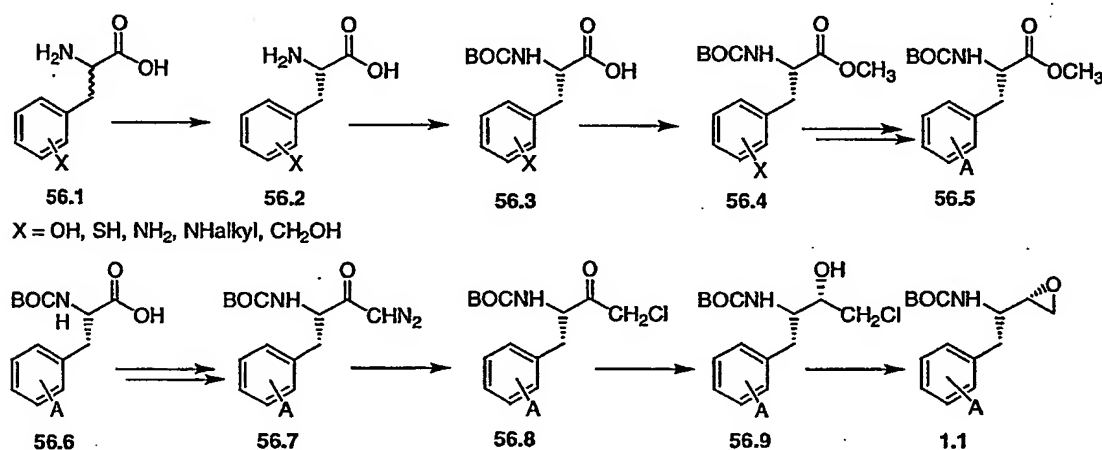
In this procedure, a protected hydroxymethyl-substituted phenylalanine 59.1 is converted into the halomethyl-substituted compound 59.2. For example, the carbinol 59.1 is treated with triphenylphosphine and carbon tetrabromide, as described in J. Am. Chem. Soc., 108, 1035, 1986 to afford the product 59.2 in which Z is Br. The bromo compound is then reacted with a dialkyl terminally hetero-substituted alkylphosphonate 59.3. The reaction is accomplished in the presence of a base, the nature of which depends on the nature of the substituent X. For example, if X is SH, NH₂ or NHalkyl, an inorganic base such as cesium carbonate, or an organic base such as diazabicyclononene, can be employed. If X is OH, a strong base such as lithium hexamethyldisilylazide or the like can be employed. The condensation reaction affords the phosphonate-substituted ester 59.4, which, employing the sequence of reactions shown in Scheme 56, is transformed into the epoxide 59.5.

For example, the protected 4-hydroxymethyl-substituted phenylalanine derivative 59.6, obtained from the 4-hydroxymethyl phenylalanine, the preparation of which is described in

Syn. Comm., 1998, 28, 4279, is converted into the bromo derivative **59.7**, as described above. The product is then reacted with a dialkyl 2-aminoethyl phosphonate **59.8**, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in the presence of cesium carbonate in dimethylformamide at ambient temperature, to afford the amine product **59.9**. The latter
 5 compound is then converted, using the sequence of reactions shown in Scheme 56, into the epoxide **59.10**.

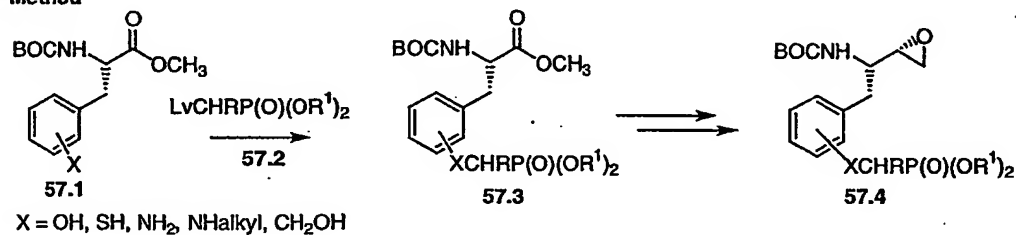
Using the above procedures, but employing different carbinols **59.1** in place of **59.6**, and/or different phosphonates **59.3**, the corresponding products **59.5** are obtained.

Scheme 56

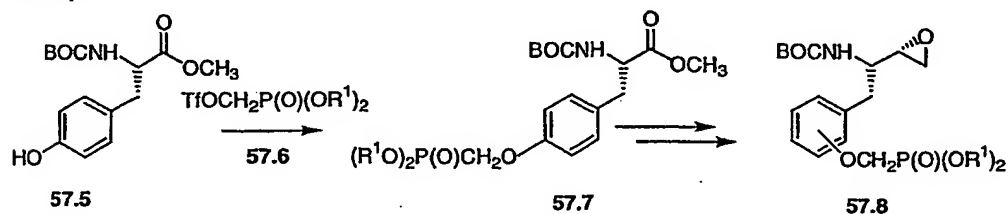


Scheme 57

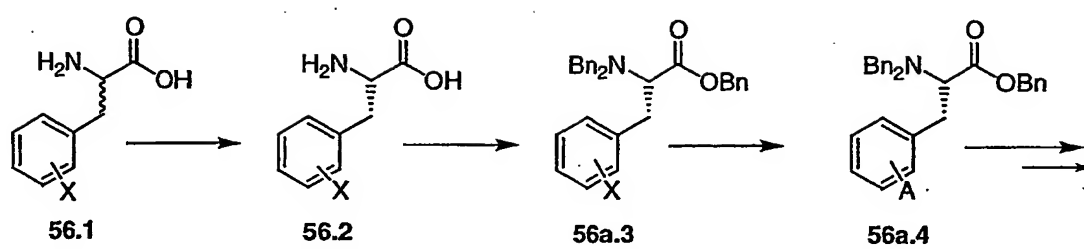
Method



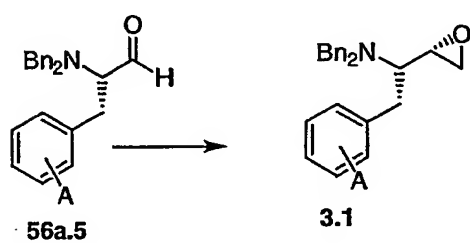
Example



Scheme 56a

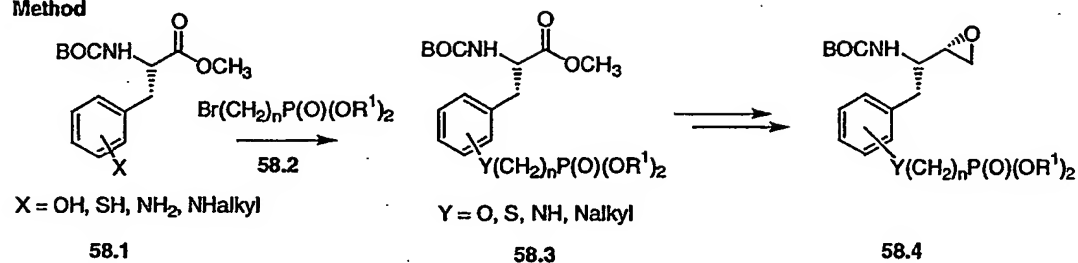


X = OH, SH, NH₂, NHalkyl, CH₂OH

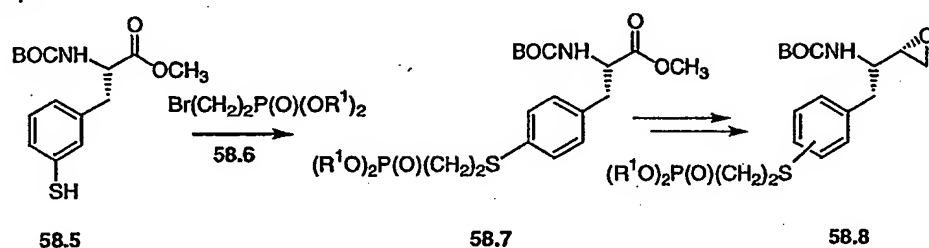


Scheme 58

Method

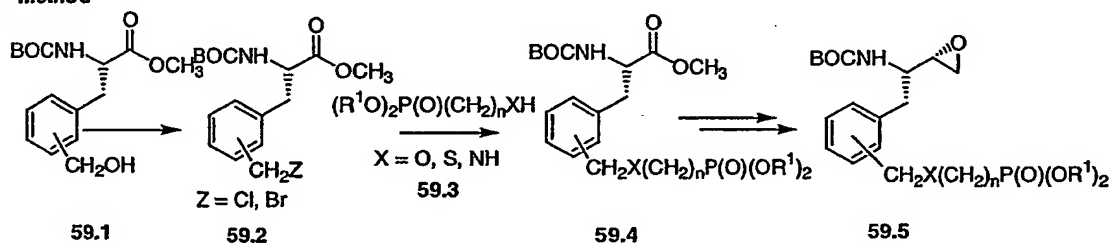


Example

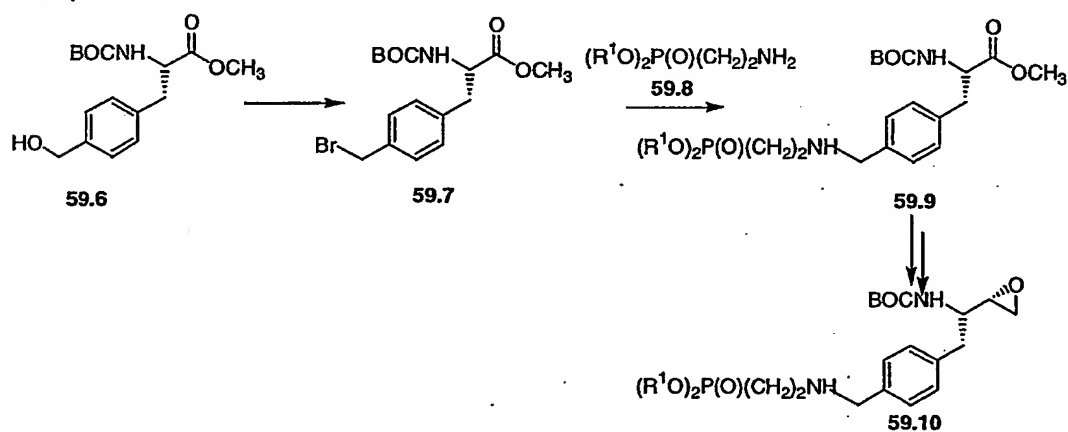


Scheme 59

Method



Example



Preparation of phenylalanine derivatives 2.1 incorporating phosphonate moieties or precursors thereto.

Scheme 60 illustrates the preparation of the hydroxymethyl oxazolidine derivative 2.1, in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc. In this reaction sequence, the substituted phenylalanine 60.1, in which A is as defined above, is transformed, via the intermediates 60.2 - 60.9, into the hydroxymethyl product 2.1. In this procedure, phenylalanine, or a substituted derivative thereof, 60.1, is converted into the phthalimido derivative 60.2. The conversion of amines into phthalimido derivatives is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 358. The amine is reacted with phthalic anhydride, 2-carboethoxybenzoyl chloride or N-carboethoxyphthalimide, optionally in the presence of a base such as triethylamine or sodium carbonate, to afford the protected amine 60.2. Preferably, the aminoacid is reacted with phthalic anhydride in toluene at reflux, to yield the phthalimido product. The carboxylic acid is then transformed into an activated derivative such as the acid chloride 60.3, in which X is Cl. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of a tertiary amide such as dimethylformamide. Preferably, the carboxylic acid is transformed into the acid chloride by reaction with oxalyl chloride and a catalytic amount of dimethylformamide, in toluene solution at ambient temperature, as described in WO 9607642. The acid chloride 60.3, X = Cl, is then converted into the aldehyde 60.4 by means of a reduction reaction. This procedure is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 620. The transformation can be effected by means of catalytic hydrogenation, a procedure which is referred to as the Rosenmund reaction, or by chemical reduction employing, for example, sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride or triethylsilane. Preferably, the acid chloride 60.3 X = Cl, is hydrogenated in toluene solution over a 5% palladium on carbon catalyst, in the presence of butylene oxide, as described in WO 9607642, to afford the aldehyde 60.4. The aldehyde 60.4 is then transformed into the cyanohydrin derivative 60.5. The conversion of aldehydes into cyanohydrins is described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 211. For example, the aldehyde 60.4 is converted into the cyanohydrin 60.5 by reaction with trimethylsilyl cyanide in an inert solvent such as dichloromethane, followed by treatment with an organic acid such as citric acid, as described

in WO 9607642, or by alternative methods described therein. The cyanohydrin is then subjected to acidic hydrolysis, to effect conversion of the cyano group into the corresponding carboxy group, with concomitant hydrolysis of the phthalimido substituent to afford the aminoacid **60.6**. The hydrolysis reactions are effected by the use of aqueous mineral acid. For example, the substrate **60.5** is reacted with aqueous hydrochloric acid at reflux, as described in WO 9607642, to afford the carboxylic acid product **60.6**. The aminoacid is then converted into a carbamate, for example the ethyl carbamate **60.7**. The conversion of amines into carbamates is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 317. The amine is reacted with a chloroformate, for example ethyl chloroformate, in the presence of a base such as potassium carbonate, to afford the carbamate **60.7**. For example, the aminoacid **60.6** is reacted, in aqueous solution, with ethyl chloroformate and sufficient aqueous sodium hydroxide to maintain a neutral pH, as described in WO 9607642, to afford the carbamate **60.7**. The latter compound is then transformed into the oxazolidinone **60.8**, for example by treatment with aqueous sodium hydroxide at ambient temperature, as described in WO 9607642. The resultant carboxylic acid is transformed into the methyl ester **60.9** by means of a conventional esterification reaction. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and an alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and an alkyl halide, for example an alkyl bromide. For example, the carboxylic acid **60.8** is converted into the methyl ester **60.9** by treatment with methanol at reflux temperature, in the presence of a catalytic amount of sulfuric acid, as described in WO 9607642. The carbomethoxyl group present in the compound **60.9** is then reduced to yield the corresponding carbinol **2.1**. The reduction of carboxylic esters to the carbinols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 550. The transformation can be effected by the use of reducing agents such as borane-dimethylsulfide, lithium borohydride, diisobutyl aluminum hydride, lithium aluminum hydride and the like. For example, the ester **60.9** is reduced to the carbinol **2.1** by reaction with sodium borohydride in ethanol at ambient temperature, as described in WO 9607642.

The conversion of the substituent A into the group link-P(O)(OR¹)₂ may be effected at any convenient step in the reaction sequence, or after the reactant **2.1** has been incorporated into

the intermediates 1. Specific examples of the preparation of the hydroxymethyl oxazolidinone reactant 2.1 are shown below, (Schemes 61-62)

Scheme 61 depicts the preparation of hydroxymethyloxazolidinones 61.9 in which the
5 phosphonate ester moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 61.1 is converted, using the series of reactions illustrated in Scheme 60, into the bromophenyloxazolidinone 61.2. The bromophenyl compound is then coupled, in the presence of a palladium (0) catalyst, with a dialkyl phosphite 61.3, to afford the
10 phosphonate product 61.4. The reaction between aryl bromide and dialkyl phosphites to yield aryl phosphonates is described in Synthesis, 56, 1981, and in J. Med. Chem., 1992, 35, 1371. The reaction is conducted in an inert solvent such as toluene or xylene, at about 100°, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium and a tertiary organic base such as triethylamine. The carbomethoxy substituent in the resultant phosphonate ester 61.4 is then reduced with sodium borohydride to the corresponding
15 hydroxymethyl derivative 61.5, using the procedure described above (Scheme 60). For example, 3-bromophenylalanine 61.6, prepared as described in Pept. Res., 1990, 3, 176, is converted, using the sequence of reactions shown in Scheme 60, into 4-(3-bromo-benzyl)-2-oxo-oxazolidine-5-carboxylic acid methyl ester 61.7. This compound is then coupled with a
20 dialkyl phosphite 61.3, in toluene solution at reflux, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to afford the phosphonate ester 61.8. The carbomethoxy substituent is then reduced with sodium borohydride, as described above, to afford the hydroxymethyl product 61.9. Using the above procedures, but employing, in place of 3-bromophenylalanine 61.6 different bromophenylalanines 61.1 and/or different dialkyl phosphites 61.3, the corresponding products
25 61.5 are obtained.

Scheme 62 illustrates the preparation of phosphonate-containing hydroxymethyl oxazolidinones 62.9 and 62.12 in which the phosphonate group is attached by means of a heteroatom and a carbon chain. In this sequence of reactions, a hydroxy or thio-substituted
30 phenylalanine 62.1 is converted into the benzyl ester 62.2 by means of a conventional acid catalyzed esterification reaction. The hydroxyl or mercapto group is then protected. The protection of phenyl hydroxyl and thiol groups are described, respectively, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, and p. 277. For example, hydroxyl and thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the phenol or thiophenol with a chlorotrialkylsilane and a base such as imidazole, for example as described in

5 Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974. The protected ester 62.3 is then reacted

10 with phthalic anhydride, as described above (Scheme 60) to afford the phthalimide 62.4. The benzyl ester is then removed, for example by catalytic hydrogenation or by treatment with aqueous base, to afford the carboxylic acid 62.5. This compound is transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy oxazolidinone 62.6, using in each step the same conditions as are described above (Scheme 60). The protected OH or

15 SH group is then deprotected. Deprotection of phenols and thiophenols is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. For example, trialkylsilyl ethers or thioethers can be deprotected by treatment with a tetraalkylammonium fluoride in an inert solvent such as tetrahydrofuran, as described in J. Am Chem. Soc., 94, 6190, 1972. Tert-butyl or adamantyl thioethers can be converted into

20 the corresponding thiols by treatment with mercuric trifluoroacetate in aqueous acetic acid at ambient temperatures, as described in Chem. Pharm. Bull., 26, 1576, 1978. The resultant phenol or thiol 62.7 is then reacted with a hydroxyalkyl phosphonate 62.20 under the conditions of the Mitsunobu reaction, as described above (Scheme 49), to afford the ether or thioether 62.8. The latter compound is then reduced with sodium borohydride, as described

25 above (Scheme 60) to afford the hydroxymethyl analog 62.9.

Alternatively, the phenol or thiophenol 62.7 is reacted with a dialkyl bromoalkyl phosphonate 62.10 to afford the alkylation product 62.11. The alkylation reaction is performed in a polar organic solvent such as dimethylformamide, acetonitrile and the like, optionally in the presence of potassium iodide, and in the presence of an inorganic base such as potassium or cesium

30 carbonate, or an organic base such as diazabicyclononene or dimethylaminopyridine. The ether or thioether product is then reduced with sodium borohydride to afford the hydroxymethyl compound 62.12.

For example, 3-hydroxyphenylalanine **62.13** (Fluka) is converted in to the benzyl ester **62.14** by means of a conventional acid-catalyzed esterification reaction. The ester is then reacted with tert-butylchlorodimethylsilane and imidazole in dimethylformamide, to afford the silyl ether **62.15**. The protected ether is then reacted with phthalic anhydride, as described above
5 (Scheme 60) to yield the phthalimido-protected compound **62.16**. Basic hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, then affords the carboxylic acid **62.17**. This compound is then transformed, by means of the series of reactions shown in Scheme 60, into the carbomethoxy-substituted oxazolidinone **62.18**. The silyl protecting group is then removed by treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient
10 temperature, to produce the phenol **62.19**. The latter compound is reacted with a dialkyl hydroxymethyl phosphonate **62.20** diethylazodicarboxylate and triphenylphosphine, by means of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and
15 R. J. Sundberg, Plenum, 2001, p. 153-4 and in Org. React., 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in Org. React., 1992, 42, 335-656. The reaction yields the phenolic ether **62.21**. The carbomethoxy group is then
20 reduced by reaction with sodium borohydride, as described above, to afford the carbinol **62.22**.

Using the above procedures, but employing, in place of 3-hydroxyphenylalanine **62.13**, different hydroxy or mercapto-substituted phenylalanines **62.1**, and/or different dialkyl hydroxyalkyl phosphonates **62.20**, the corresponding products **62.9** are obtained.

25 As a further example of the methods illustrated in Scheme 62, 4-mercaptophenylalanine **62.23**, prepared as described in J. Am. Chem. Soc., 1997, 119, 7173, is converted into the benzyl ester **62.24** by means of a conventional acid-catalyzed esterification reaction. The mercapto group is then protected by conversion to the S-adamantyl group, by reaction with 1-adamantanol and trifluoroacetic acid at ambient temperature as described in Chem. Pharm.
30 Bull., 26, 1576, 1978. The amino group is then converted into the phthalimido group as described above, and the ester moiety is hydrolyzed with aqueous base to afford the carboxylic acid **62.27**. The latter compound is then transformed, by means of the series of reactions

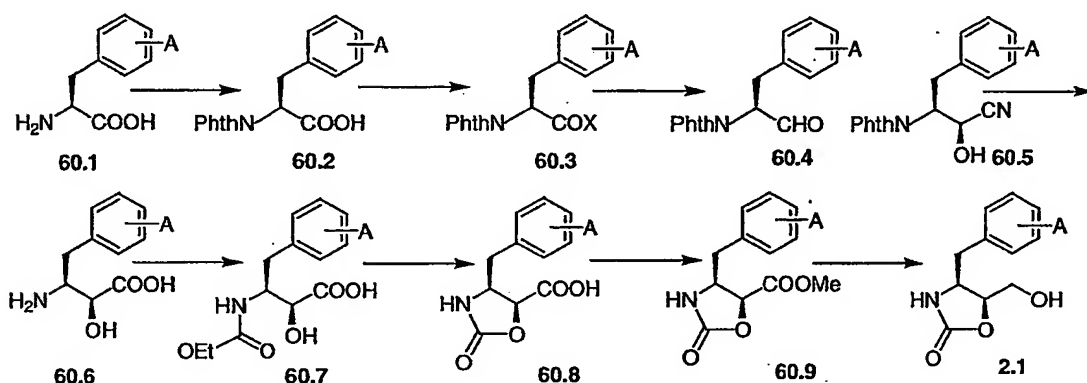
shown in Scheme 60, into the carbomethoxy oxazolidinone 62.28. The adamantyl protecting group is then removed by treatment of the thioether 62.28 with mercuric acetate in trifluoroacetic acid at 0°, as described in Chem. Pharm. Bull., 26, 1576, 1978, to produce the thiol 62.29. The thiol is then reacted with one molar equivalent of a dialkyl

- 5 bromoethylphosphonate 62.30, (Aldrich) and cesium carbonate in dimethylformamide at 70°, to afford the thioether product 62.31. The carbomethoxy group is then reduced with sodium borohydride, as described above, to prepare the carbinol 62.32.

Using the above procedures, but employing, in place of 4-mercaptophenylalanine 62.23, different hydroxy or mercapto-substituted phenylalanines 62.1, and/or different dialkyl

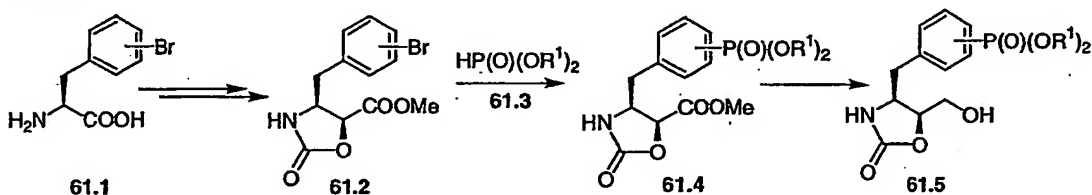
- 10 bromoalkyl phosphonates 62.10, the corresponding products 62.12 are obtained.

Scheme 60

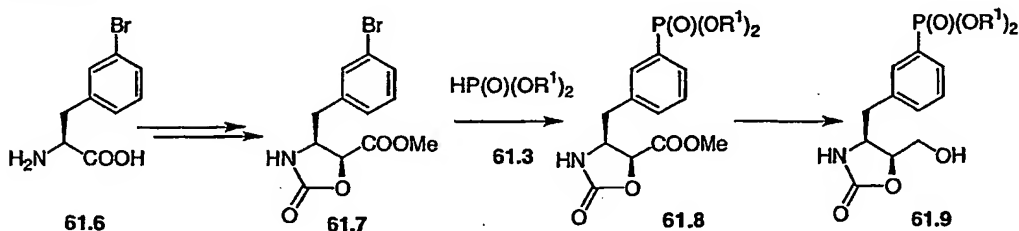


Scheme 61

Method

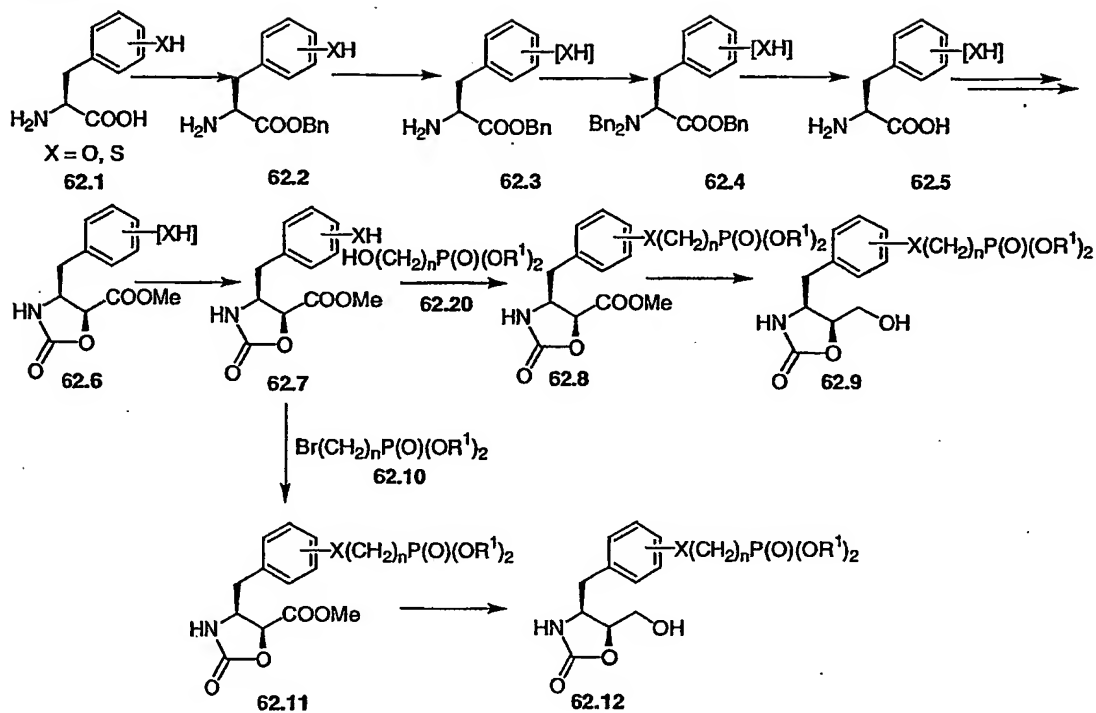


Example

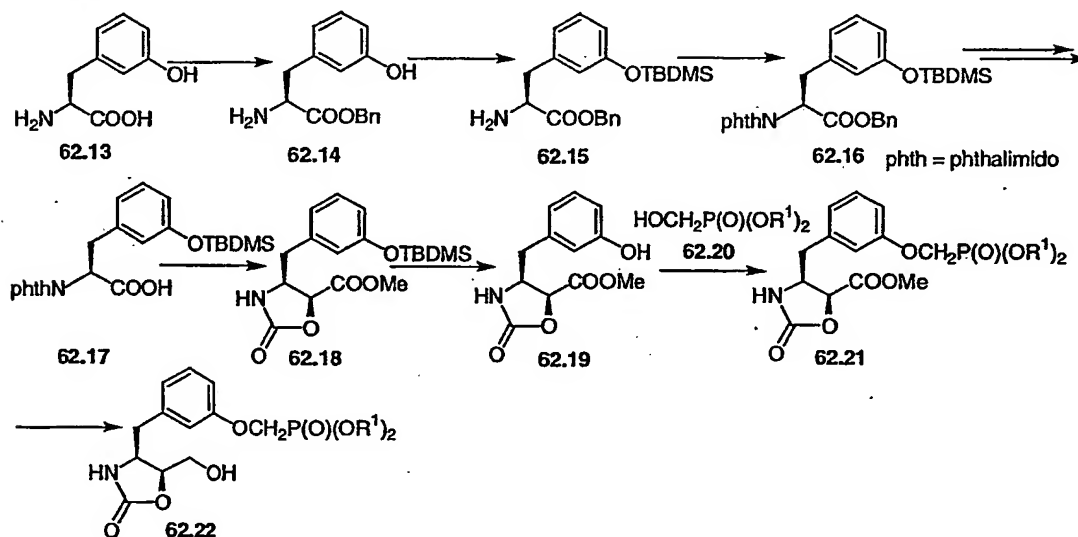


Scheme 62

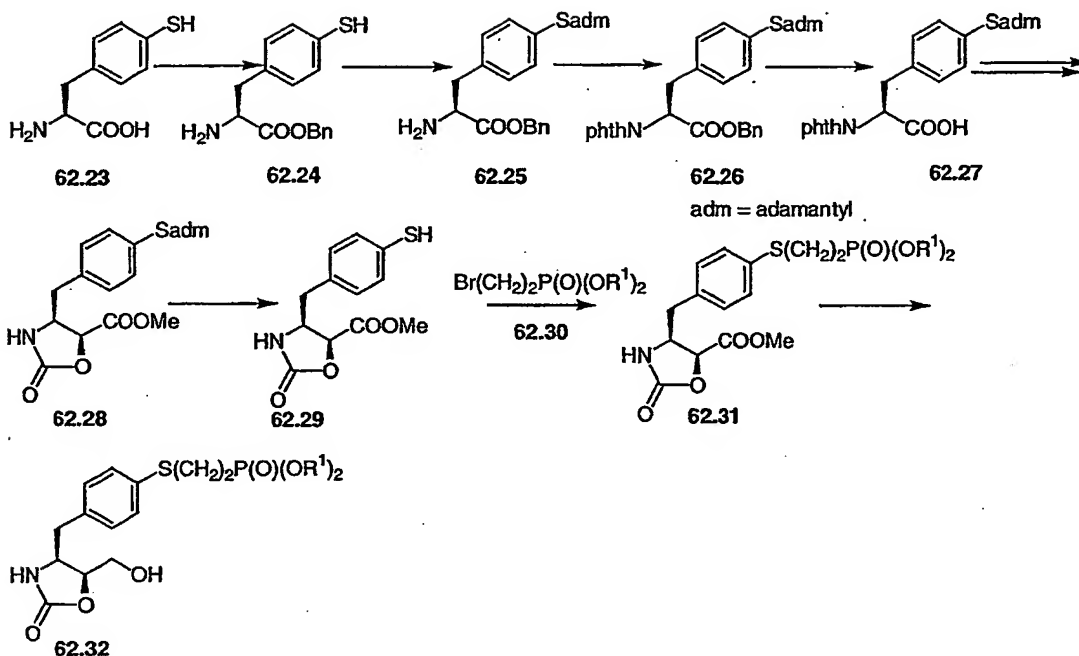
Method



Scheme 62 Example 1



Scheme 62 Example 2



Preparation of the phosphonate-containing thiophenol derivatives 7.2.

- 5 Schemes 63 - 83 describe the preparation of phosphonate-containing thiophenol derivatives 7.2 which are employed as described above (Schemes 7 - 9) in the preparation of the phosphonate ester intermediates 1 in which X is sulfur.

- 10 Scheme 63 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 63.1 is protected to afford the product 63.2. The protection of phenyl thiol groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 277. For example, thiol substituents can be protected as trialkylsilyloxy groups. Trialkylsilyl groups are introduced by the reaction of the thiophenol with a
- 15 chlorotrialkylsilane and a base such as imidazole, for example as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 10, p. 68-86. Alternatively, thiol substituents can be protected by conversion to tert-butyl or adamantyl thioethers, or 4-methoxybenzyl thioethers, prepared by the reaction between the thiol and 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in

Bull. Chem. Soc. Jpn., 37, 433, 1974. The product is then coupled, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, with a dialkyl phosphite 63.3, to afford the phosphonate ester 63.4. The thiol protecting group is then removed, as described above, to afford the thiol 63.5.

- 5 For example, 3-bromothiophenol 63.6 is converted into the 9-fluorenylmethyl (Fm) derivative 63.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 63.3, as described above, to afford the phosphonate ester 63.8. The Fm protecting group is then removed by treatment of the product with piperidine in
10 dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 63.9.

Using the above procedures, but employing, in place of 3-bromothiophenol 63.6, different thiophenols 63.1, and/or different dialkyl phosphites 63.3, the corresponding products 63.5 are obtained.

15

- Scheme 64 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 64.2 is metallated, for example by reaction with magnesium or by transmetallation with an alkyllithium reagent, to afford the metallated derivative 64.3. The latter compound is reacted
20 with a halodialkyl phosphite 64.4 to afford the product 64.5; deprotection then affords the thiophenol 64.6

- For example, 4-bromothiophenol 64.7 is converted into the S-triphenylmethyl (trityl) derivative 64.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 64.9
25 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite 64.10 to afford the phosphonate 64.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 64.12.

- Using the above procedures, but employing, in place of the bromo compound 64.7, different
30 halo compounds 64.1, and/or different halo dialkyl phosphites 64.4, there are obtained the corresponding thiols 64.6.

Scheme 65 illustrates the preparation of phosphonate-substituted thiophenols in which the phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 65.1 is subjected to free-radical bromination to afford a bromomethyl product 65.2. This compound is reacted with a sodium dialkyl phosphite 65.3 or a trialkyl phosphite, to give the displacement or rearrangement product 65.4, which upon deprotection affords the thiophenol 65.5.

For example, 2-methylthiophenol 65.6 is protected by conversion to the benzoyl derivative 65.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 65.8. This material is reacted with a sodium dialkyl phosphite 65.3, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 65.9. Alternatively, the bromomethyl compound 65.8 is converted into the phosphonate 65.9 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem., 1992, 115. In this procedure, the bromomethyl compound 65.8 is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate 65.9. Deprotection of the phosphonate 65.9, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol 65.10.

Using the above procedures, but employing, in place of the bromomethyl compound 65.8, different bromomethyl compounds 65.2, there are obtained the corresponding thiols 65.5.

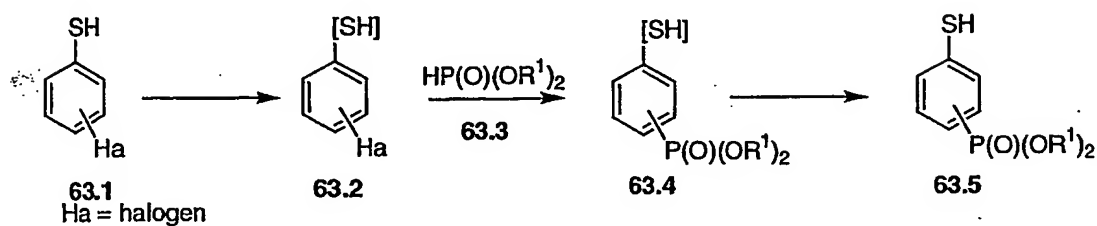
Scheme 66 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 66.1 is reacted with a dialkyl hydroxyalkylphosphonate 66.2 under the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product 66.3. Deprotection then yields the O- or S-linked products 66.4.

For example, the substrate 3-hydroxythiophenol, 66.5, is converted into the monotrityl ether 66.6, by reaction with one equivalent of trityl chloride, as described above. This compound is reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 66.7 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 66.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 66.9.

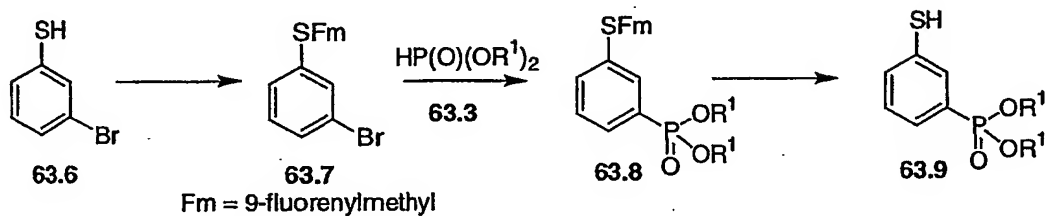
Using the above procedures, but employing, in place of the phenol **66.5**, different phenols or thiophenols **66.1**, there are obtained the corresponding thiols **66.4**.

Scheme 63

Method



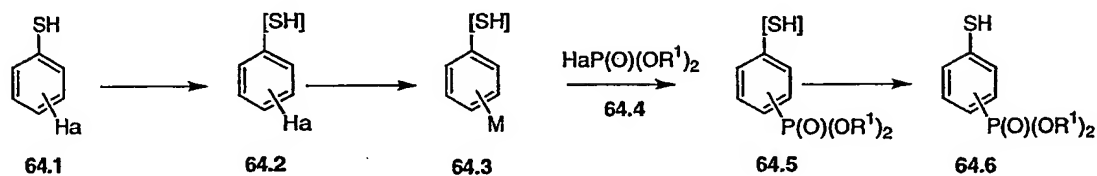
Example



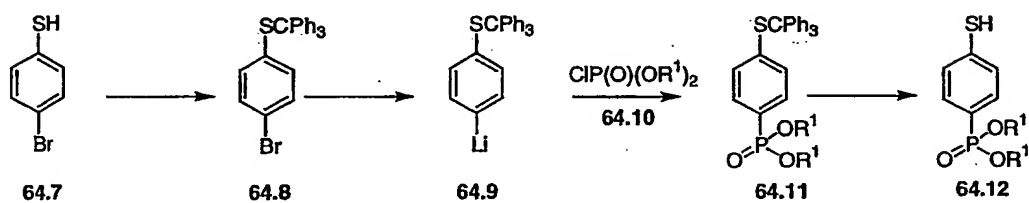
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Scheme 64

Method

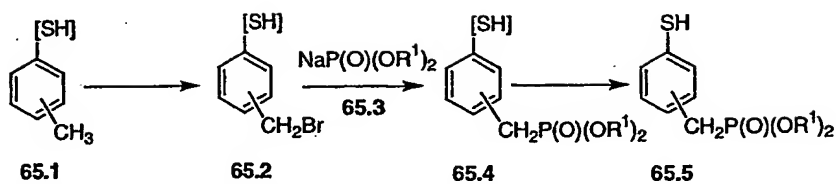


Example

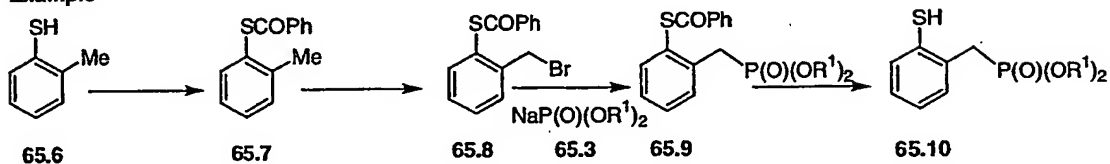


Scheme 65

Method

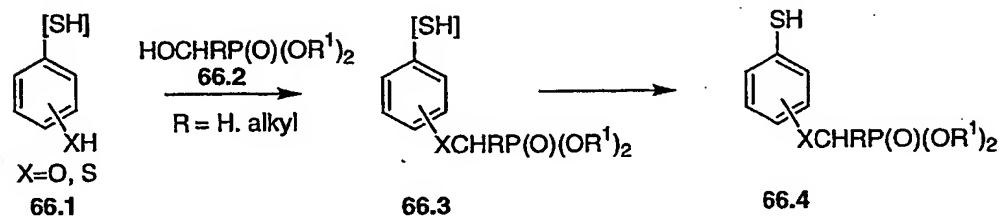


Example

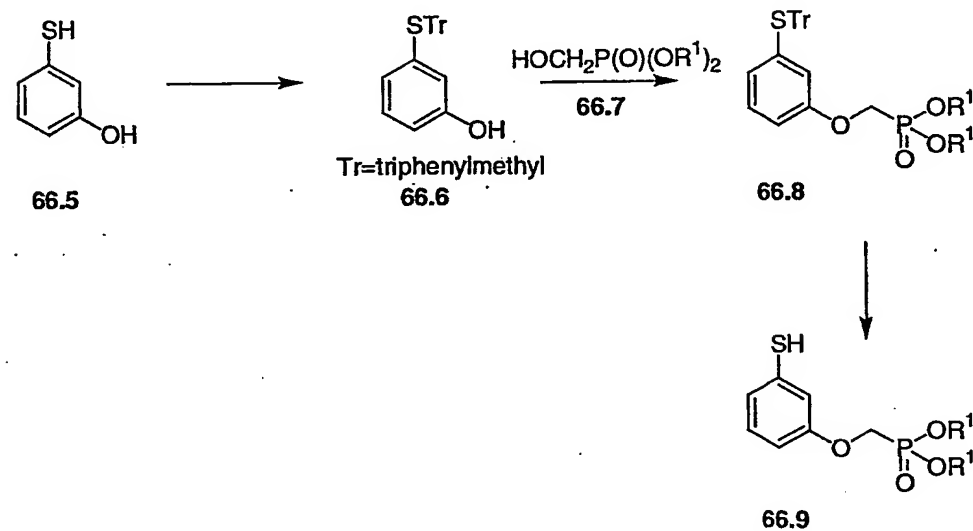


Scheme 66

Method



Example



Scheme 67 illustrates the preparation of thiophenols 67.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 67.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 67.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 67.3. Deprotection then affords the thiol 67.4.

For example, 4-methylaminothiophenol 67.5 is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product 67.6. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate 67.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 67.8. Preferably, equimolar amounts of the phosphonate 67.7 and the amine 67.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 67.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 67.9.

Using the above procedures, but employing, in place of the thioamine 67.5, different phenols, thiophenols or amines 67.1, and/or different phosphonates 67.2, there are obtained the corresponding products 67.4.

Scheme 68 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 68.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 68.1 is reacted with a dialkyl bromoalkyl phosphonate 68.2 to afford the product 68.3. Deprotection then affords the free thiophenol 68.4.

For example, 3-hydroxythiophenol 68.5 is converted into the S-trityl compound 68.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 68.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

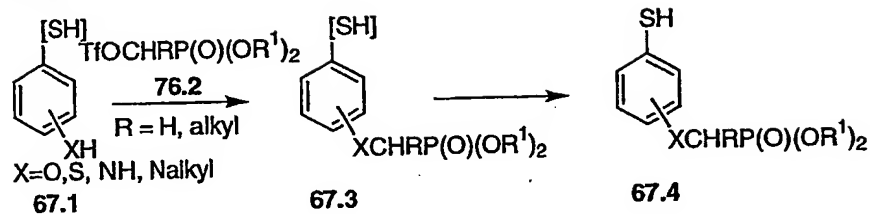
potassium iodide, at about 50°, to yield the ether product 68.8. Deprotection, as described above, then affords the thiol 68.9.

Using the above procedures, but employing, in place of the phenol 68.5, different phenols, thiophenols or amines 68.1, and/or different phosphonates 68.2, there are obtained the
5 corresponding products 68.4.

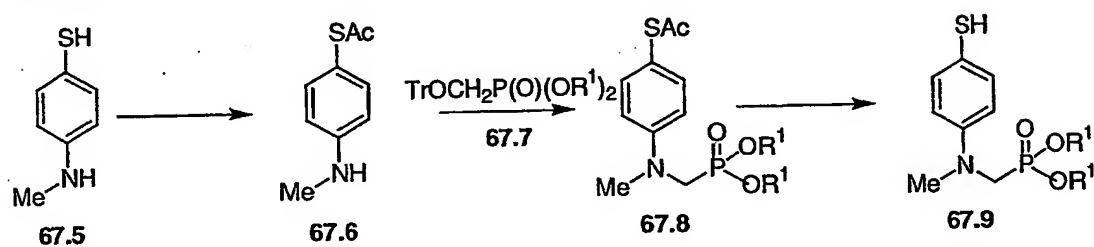
Scheme 69 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 69.2 is
10 coupled with an aromatic bromo compound 69.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
15 tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 69.3. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 69.4, or the saturated analog 69.6.
20 For example, 3-bromothiophenol is converted into the S-Fm derivative 69.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 69.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
25 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 69.9. Deprotection, as described above, then affords the thiol 69.10. Optionally, the initially formed unsaturated phosphonate 69.9 is subjected to reduction, for example using diimide, as described above, to yield the saturated product 69.11, which upon deprotection affords the thiol 69.12.
30 Using the above procedures, but employing, in place of the bromo compound 69.7, different bromo compounds 69.1, and/or different phosphonates 69.2, there are obtained the corresponding products 69.4 and 69.6

Scheme 67

Method

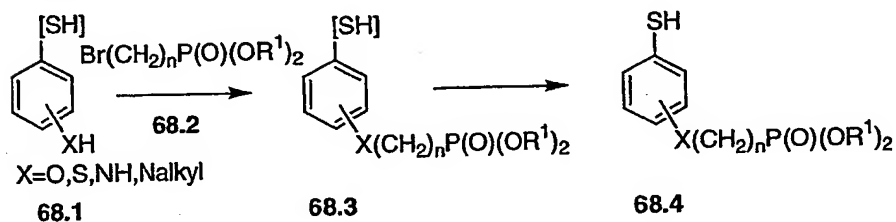


Example

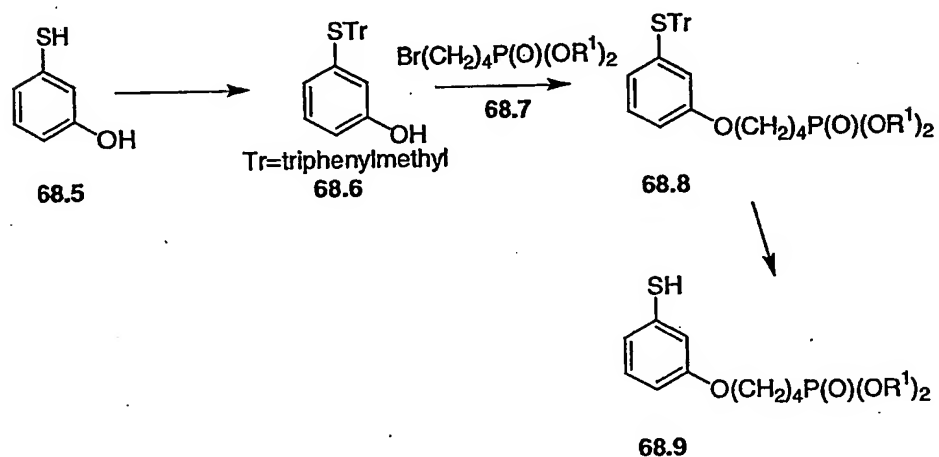


Scheme 68

Method

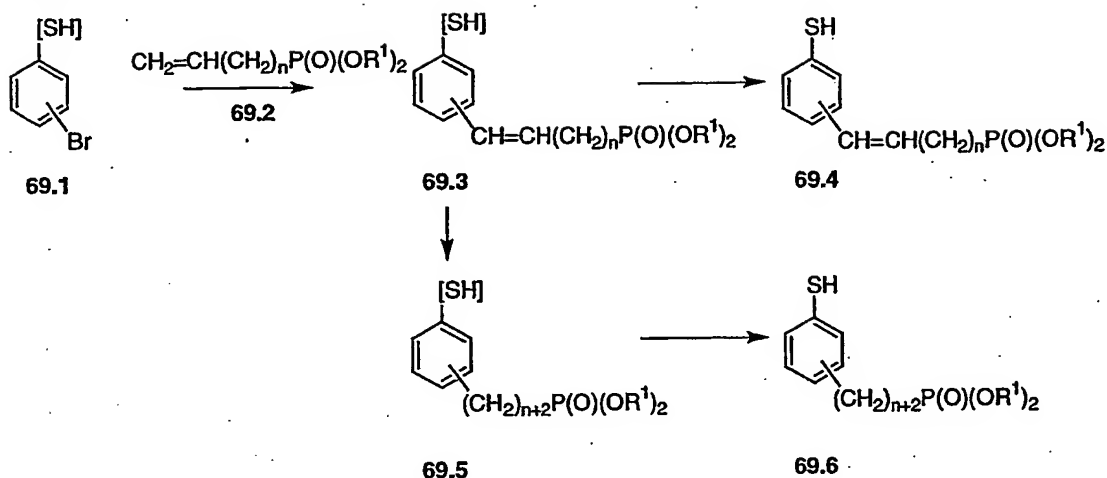


Example

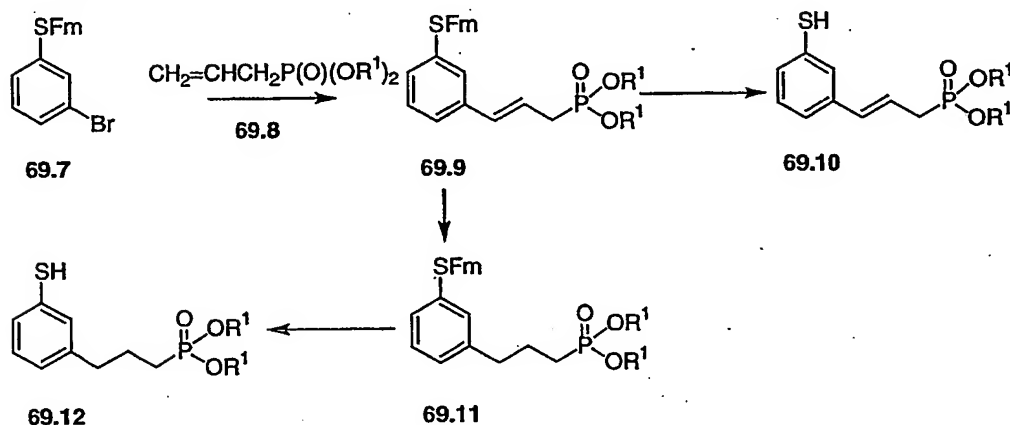


Scheme 69

Method



Example



Scheme 70 illustrates the preparation of an aryl-linked phosphonate ester **70.4** by means of a
 5 palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a
 phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock,
 VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid **70.1** is obtained by means of a
 metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for
 example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the
 10 diaryl product **70.3** which is deprotected to yield the thiol **70.4**.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane,
 in the presence of a base such as imidazole, as described in Protective Groups in Organic

Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate **70.5**. This material is reacted with a dialkyl 4-bromophenylphosphonate **70.6**, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product **70.7**. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol **70.8**. Using the above procedures, but employing, in place of the boronate **70.5**, different boronates **70.1**, and/or different phosphonates **70.2**, there are obtained the corresponding products **70.4**.

Scheme **71** depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol **71.1** is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate **71.2**, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product **71.3** is then deprotected to afford the thiol **71.4**. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester **71.5** by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol **71.5** is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, **71.6**, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The thioether product **71.7** thus obtained is deprotected, as described above, to afford the thiol **71.8**.

Using the above procedures, but employing, in place of the thiophenol **71.5**, different phenols, thiophenols or amines **71.1**, and/or different phosphonates **71.2**, there are obtained the corresponding products **71.4**.

Scheme **72** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **72.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **72.2**, in the presence of an

organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester 72.3. Deprotection, as described above, then affords the thiol 72.4. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding

5 hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in

10 J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707.

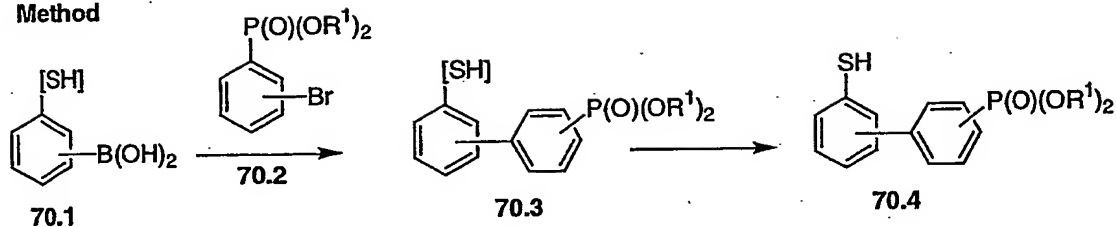
15 For example, 2,3-dihydro-1H-indole-5-thiol, 72.5, the preparation of which is described in EP 209751, is converted into the benzoyl ester 72.6, as described above, and the ester is then reacted with the trifluoromethanesulfonate 72.7, in a polar organic solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, to yield the phosphonate 72.8. Deprotection, for example by reaction with dilute aqueous ammonia, as

20 described above, then affords the thiol 72.9.

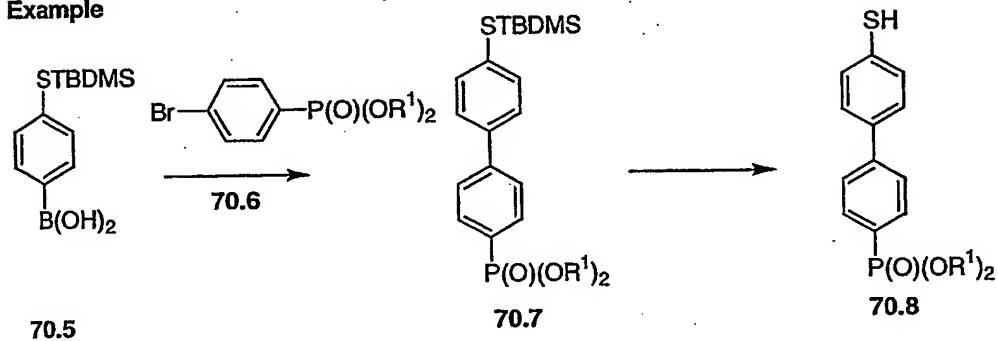
Using the above procedures, but employing, in place of the thiol 72.5, different thiols 72.1, and/or different triflates 72.2, there are obtained the corresponding products 72.4.

Scheme 70

Method

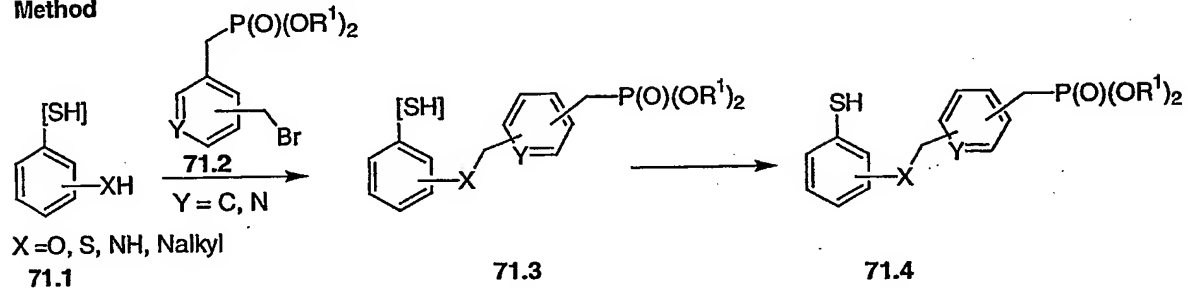


Example

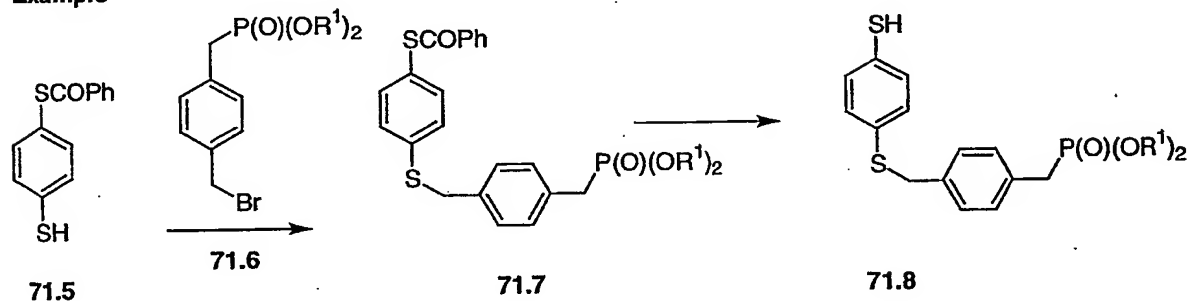


Scheme 71

Method



Example



5 Preparation of phosphonate-containing analogs of isobutylamine 10.2.

Schemes 73 - 75 illustrate the preparation of the phosphonate-containing analogs of isobutylamine which are employed in the preparation of the phosphonate esters 2.

Scheme 73 depicts the preparation of phosphonates which are attached to the isobutylamine by means of an amide linkage. In this procedure, an aminoacid 73.1 is protected to afford the product 73.2. The protection of amino groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, 309. Amino groups are protected, for example, by conversion into carbamates such as the tert. butoxycarbonate (BOC) derivative, or by reaction with phthalic anhydride to afford the phthalimido (phth) derivative. The amine-protected aminoacid 73.2 is then coupled with a dialkyl aminoalkyl phosphonate 73.3, to yield the amide 73.4. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The protecting group is then removed to afford the amine 73.5. Deprotection of amines is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 309ff. For example, BOC groups are removed by treatment with acids such as trifluoroacetic acid, and phthalimido groups are removed by reaction with hydrazine hydrate. For example, 2-methyl-4-aminobutyric acid 73.6 (Acros) is reacted with phthalic anhydride in refluxing toluene, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to give the phthalimido derivative 73.7. The product is coupled with a dialkyl aminoethyl phosphonate 73.8, the preparation of which is described in J. Org. Chem., 2000, 65, 676,

in the presence of dicyclohexyl carbodiimide, to give the amide 73.9. The protecting group is removed by reaction of the product with ethanolic hydrazine at ambient temperature, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 358, to afford the amine 73.10.

- 5 Using the above procedures, but employing, in place of the acid 73.6, different acids 73.1, and/or different amines 73.3, the corresponding amides 73.5 are obtained.

Scheme 74 depicts the preparation of isobutylamine phosphonates in which the phosphonate is attached by means of an aromatic ring. In this procedure, 2-methyl-but-3-enylamine 74.1,
10 prepared as described in Org. Prep. Proc. Int. 1976, 8, 75, is coupled, in the presence of a palladium catalyst, as described above (Scheme 50) with a dialkyl bromophenyl phosphonate 74.2 to afford the olefinic product 74.3. Optionally, the product is reduced to afford the saturated analog 74.4. The reduction is effected catalytically, for example by the use of a palladium catalyst, or chemically, for example by the use of diimide.

- 15 For example, the amine 74.1 is coupled with a dialkyl 4-bromophenyl phosphonate 74.5, prepared as described in J. Organomet. Chem., 1999, 581, 62, to yield the product 74.6. Catalytic hydrogenation in ethanol, using a 5% palladium catalyst, then affords the saturated compound 74.7.

- Using the above procedures, but employing, in place of the phosphonate 74.5, different
20 phosphonates 74.2 the corresponding products 74.3 and 74.4 are obtained.

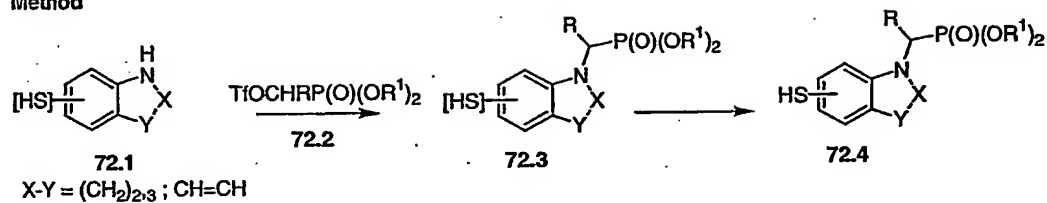
Scheme 75 illustrates the preparation of isobutylamine phosphonates in which the phosphonate group is attached by means of an alkylene chain. In this procedure, a bromoamine 75.1 is protected, as described in Scheme 73, to afford the derivative 75.2. The product is then
25 reacted with a trialkyl phosphite 75.3, in an Arbuzov reaction, as described in Scheme 65, to give the phosphonate 75.4. Deprotection then affords the amine 75.5.

For example, 4-bromo-2-methyl-butylamine 75.6, prepared as described in Tet., 1998, 54, 2365, is converted, as described above, into the phthalimido derivative 75.7. The product is then heated at 110° with a trialkyl phosphite 75.3 to yield the phosphonate 75.8, which upon
30 reaction with ethanolic hydrazine affords the amine 75.9.

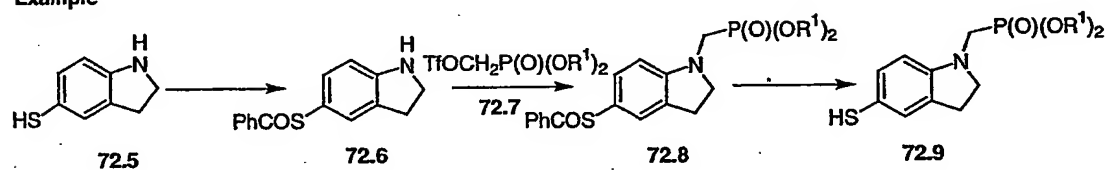
Using the above procedures, but employing, in place of the bromide 75.6, different bromides 75.1, and/or different phosphites 75.3, the corresponding products 75.5 are obtained.

Scheme 72

Method

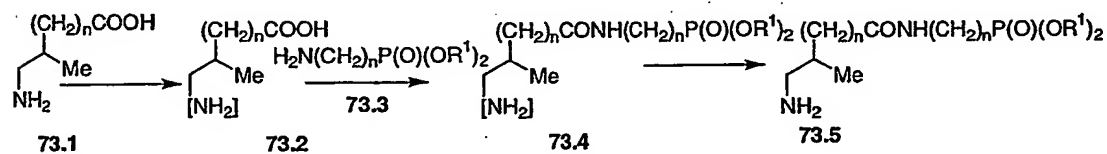


Example

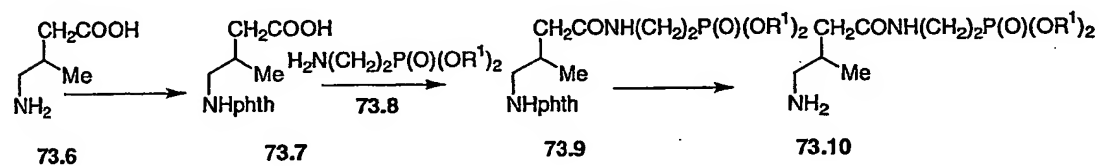


Scheme 73

Method

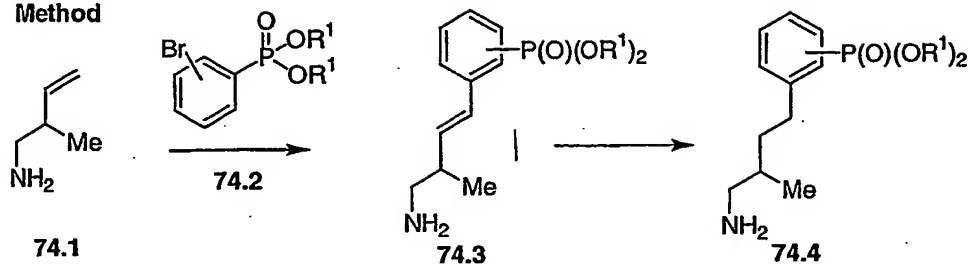


Example

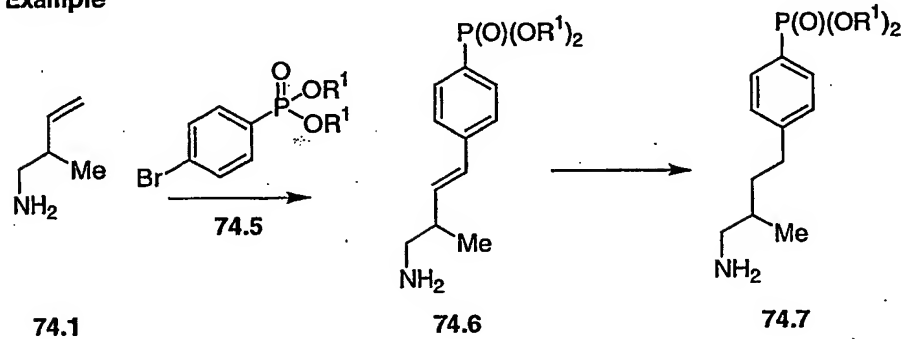


Scheme 74

Method

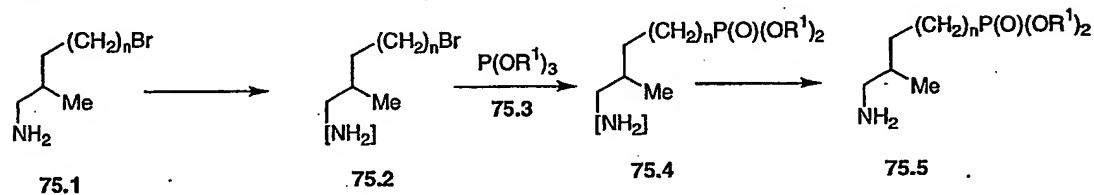


Example

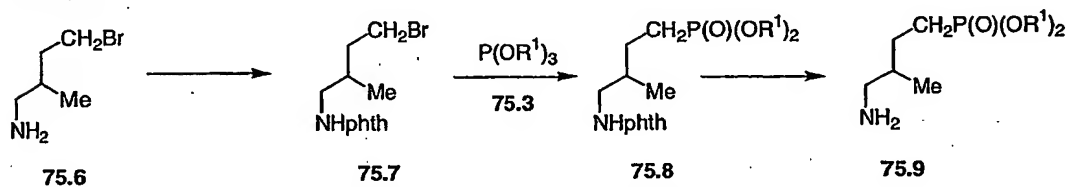


Scheme 75

Method



Example



Preparation of cyclopentylmethylamine phosphonates.

5

Schemes 76 - 78 illustrate the preparation of cyclopentylmethylamine phosphonates which are employed, as shown in Schemes 10 - 12, in the preparation of the phosphonate esters 3.

Scheme 76 depicts the preparation of phosphonates attached to the cyclopentyl ring either directly or by means of an alkoxy link. In this procedure, a hydroxy-substituted

10

- cyclopentylmethylamine **76.1** is protected, and the protected derivative **76.2** is converted into the corresponding bromide **76.3**, for example by treatment with carbon tetrabromide and triphenyl phosphine as described in Scheme 59. The bromo compound is then reacted with a trialkyl phosphite **76.4** in an Arbuzov reaction, as described above, to afford the phosphonate **76.5** which is then deprotected to give the amine **76.6**. Alternatively, the protected amine **76.2** is reacted with a dialkyl bromoalkyl phosphonate **76.7** to give the ether **76.8**. The alkylation reaction is conducted at ca 100° in a polar organic solvent such as dimethylformamide in the presence of a base such as sodium hydride or lithium hexamethyl disilylazide. The product is then deprotected to give the amine **76.9**.
- 10 For example, 3-aminomethyl-cyclopentanol **76.10**, prepared as described in Tet., 1999, 55, 10815, is converted, as described above, into the phthalimido derivative **76.11**. The product is then converted, as described above, into the bromo analog **76.12**. The latter compound is reacted at ca 120° with a trialkyl phosphite **76.4** to afford the phosphonate **76.13**, which upon deprotection by reaction with hydrazine yields the amine **76.14**.
- 15 Using the above procedures, but employing, in place of the bromide **76.12**, different bromides **76.3**, and/or different phosphites **76.4**, the corresponding products **76.6** are obtained. Alternatively, 2-aminomethyl-cyclopentanol **76.15**, prepared as described in Tet., 1999, 55, 10815, is converted into the phthalimido derivative **76.16**. The product is then reacted in dimethylformamide solution with an equimolar amount of a dialkyl bromopropyl phosphonate **76.17**, prepared as described in J. Am. Chem. Soc., 2000, 122, 1554, and sodium hydride, to
- 20 give the ether **76.18**. Deprotection, as described above, then affords the amine **76.19**. Using the above procedures, but employing, in place of the carbinol **76.15**, different carbinols **76.1**, and/or different phosphonates **76.7**, the corresponding products **76.9** are obtained.
- 25 Scheme 77 illustrates the preparation of cyclopentylmethylenamines in which the phosphonate group is attached by means of an amide group. In this procedure, a carboxyalkyl-substituted cyclopentylmethylamine **77.1** is protected to afford the derivative **77.2**. The product is then coupled, as described above, (Scheme 1) with a dialkyl aminoalkyl phosphonate **77.3** to yield the amide **77.4**. Deprotection then affords the amine **77.5**.
- 30 For example, 3-aminomethyl-cyclopentanecarboxylic acid **77.6** prepared as described in J. Chem. Soc. Perkin 2, 1995, 1381, is converted into the BOC derivative **77.7**, by reaction with BOC anhydride in aqueous sodium hydroxide, as described in Proc. Nat. Acad. Sci., 69, 730,

1972. The product is then coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminopropyl phosphonate 77.8 to produce the amide 77.9. Removal of the BOC group, for example by treatment with hydrogen chloride in ethyl acetate, then affords the amine 77.10. Using the above procedures, but employing, in place of the carboxylic acid 77.6, different carboxylic acids 77.1, and/or different phosphonates 77.3, the corresponding products 77.5 are obtained.

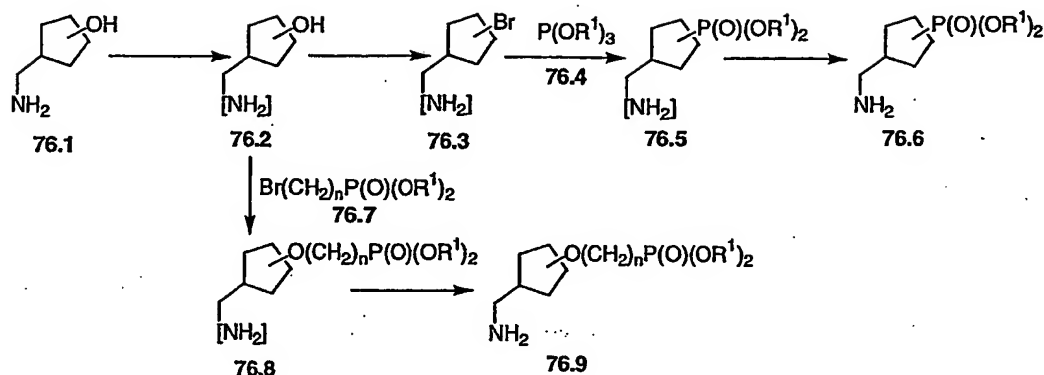
Scheme 78 illustrates the preparation of cyclopentylmethyamines in which the phosphonate group is attached by means of an aminoalkyl group. In this procedure, the more reactive amino group of an amino-substituted cyclopentylmethyamine 78.1 is protected, to give the derivative 78.2. The product is then coupled, by means of a reductive amination reaction, as described in Scheme 55, with a dialkyl formylalkyl phosphonate 78.3 to give the amine product 78.4, which upon deprotection affords the amine 78.5.

For example, 2-aminomethyl-cyclopentylamine 78.6 prepared as described in WO 9811052, is reacted with one molar equivalent of phthalic anhydride in refluxing tetrahydrofuran, to yield the phthalimido derivative 78.7. The latter compound is reacted, in the presence of sodium cyanoborohydride, with a dialkyl formylmethyl phosphonate 78.8, prepared as described in Zh. Obschei. Khim., 1987, 57, 2793, to afford the product 78.9. Deprotection, as described above, then yields the amine 78.10.

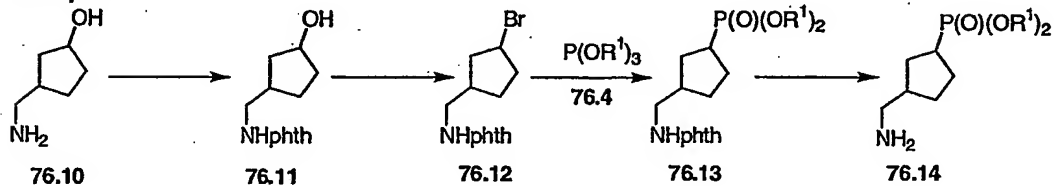
Using the above procedures, but employing, in place of the diamine 78.6, different diamines 78.1, and/or different phosphonates 78.3, the corresponding products 78.5 are obtained.

Scheme 76

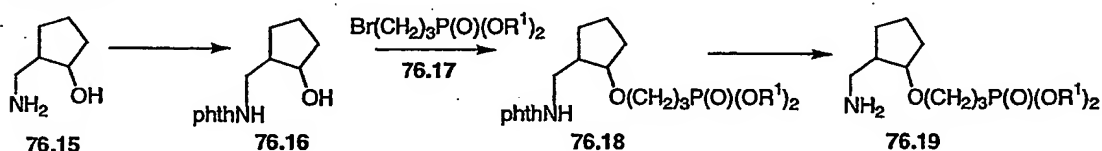
Method



Example 1

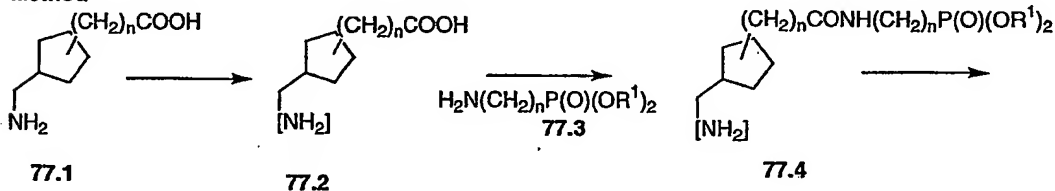


Example 2



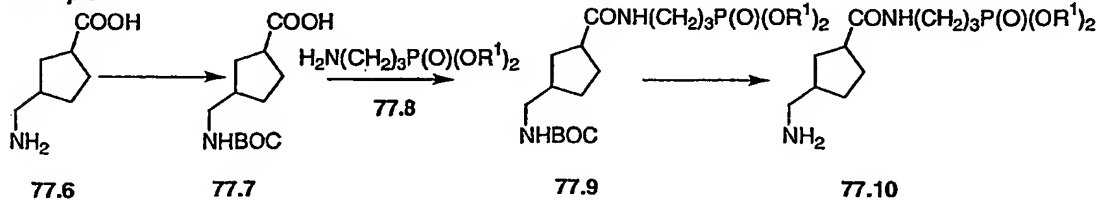
Scheme 77

Method



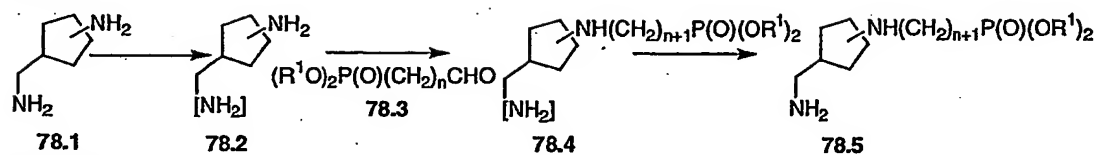
Example 5

Example

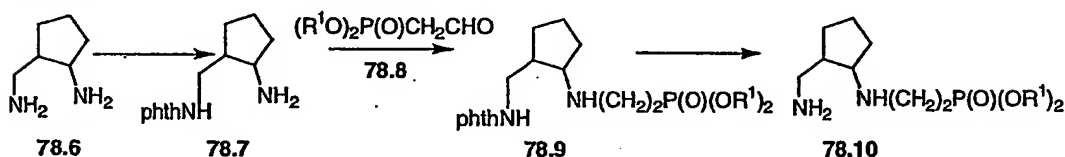


Scheme 78

Method



Example



Preparation of phosphonate-substituted fluorobenzylamines 39.2.

5

Schemes 79 and 80 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines 39.2 which are used in the preparation of the phosphonate esters 6.

Scheme 79 depicts the preparation of fluorobenzylamines in which the phosphonate is attached by means of an amide or aminoalkyl linkage. In this procedure, the more reactive amino group in an amino-substituted 3-fluorobenzylamine 79.1 is protected. The product 79.2 is then coupled with a dialkyl carboxyalkyl phosphonate 79.3 to give the amide 79.4, which upon deprotection yields the free amine 79.5. Alternatively, the mono-protected diamine 79.2 is coupled, under reductive amination conditions, with a dialkyl formylalkyl phosphonate 79.6, to produce the amine 79.7, which upon deprotection affords the benzylamine 79.8.

For example, 4-amino-3-fluorobenzylamine 79.9, prepared as described in WO 9417035, is reacted in pyridine solution with one molar equivalent of acetic anhydride, to give the acetilamino product 79.10. The product is reacted with a dialkyl carboxyethyl phosphonate 79.11, (Epsilon) and dicyclohexyl carbodiimide, to afford the amide 79.12. Deprotection, for example by reaction with 85% hydrazine, as described in J. Org. Chem., 43, 4593, 1978; then gives the amine 79.13.

Using the above procedures, but employing, in place of the diamine 79.9, different diamines 79.1, and/or different phosphonates 79.3, the corresponding products 79.5 are obtained.

As a further example, the mono-protected diamine 79.10 is reacted, as described above, with a dialkyl formyl phosphonate 79.13, (Aurora) and sodium cyanoborohydride, to give the amination product 79.14. Deprotection then affords the amine 79.15.

Using the above procedures, but employing, in place of the diamine 79.10 different diamines 79.2, and/or different phosphonates 79.6, the corresponding products 79.8 are obtained.

Scheme 80 depicts the preparation of fluorobenzylamines in which the phosphonate is attached
5 either directly or by means of a saturated or unsaturated alkylene linkage. In this procedure, a bromo-substituted 3-fluorobenzylamine 80.1 is protected. The product 80.2 is coupled, by means of a palladium-catalyzed Heck reaction, as described in Scheme 50, with a dialkyl alkenyl phosphonate 80.3, to give the olefinic product 80.4 which upon deprotection affords the amine 80.5. Optionally, the double bond is reduced, for example by catalytic
10 hydrogenation over a palladium catalyst, to yield the saturated analog 80.9. Alternatively, the protected bromobenzylamine 80.6 is coupled, as described in Scheme 61, in the presence of a palladium catalyst, with a dialkyl phosphite 80.6 to produce the phosphonate 80.7.

Deprotection then affords the amine 80.8.

For example, 2-bromo-5-fluorobenzylamine 80.10, (Esprix Fine Chemicals) is converted, as
15 described above, into the N-acetyl derivative 80.11. The product is then coupled in dimethylformamide solution with a dialkyl vinyl phosphonate 80.12, (Fluka) in the presence of palladium (II) acetate and triethylamine, to give the coupled product 80.13. Deprotection then affords the amine 80.14 and hydrogenation of the latter compound yields the saturated analog 80.15.

20 Using the above procedures, but employing, in place of the bromo compound 80.10 different bromo compounds 80.1, and/or different phosphonates 80.3, the corresponding products 80.5 and 80.9 are obtained.

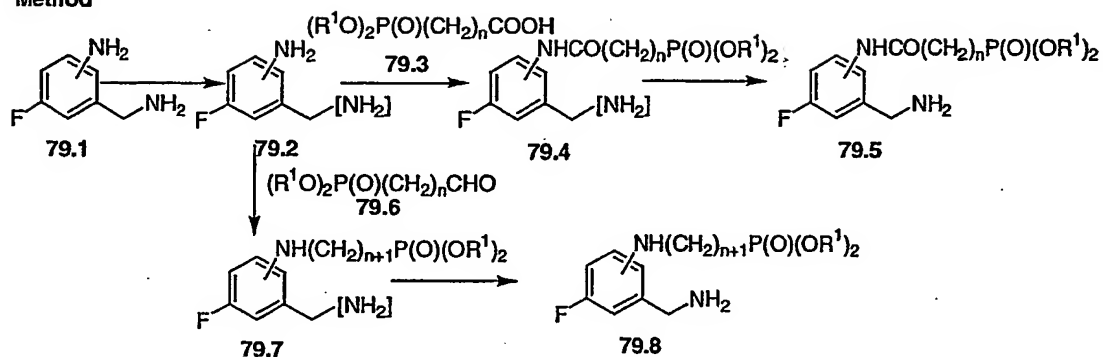
As a further example, the protected amine 80.11 is coupled, in toluene at 100°, with a dialkyl phosphite 80.6, in the presence of tetrakis(triphenylphosphine)palladium and a tertiary organic
25 base such as triethylamine, to give the phosphonate 80.16. Deprotection then affords the amine 80.17.

Using the above procedures, but employing, in place of the bromo compound 80.11 different bromo compounds 80.2, and/or different phosphites 80.6, the corresponding products 80.8 are obtained.

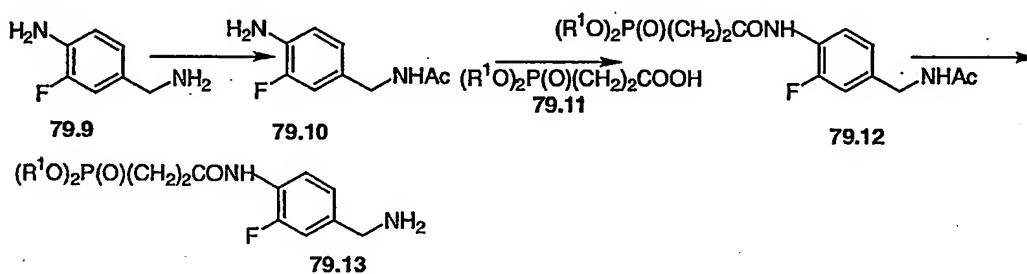
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Scheme 79

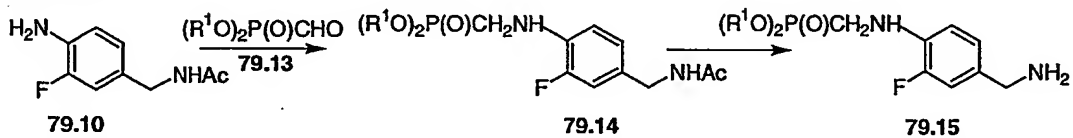
Method



Example 1

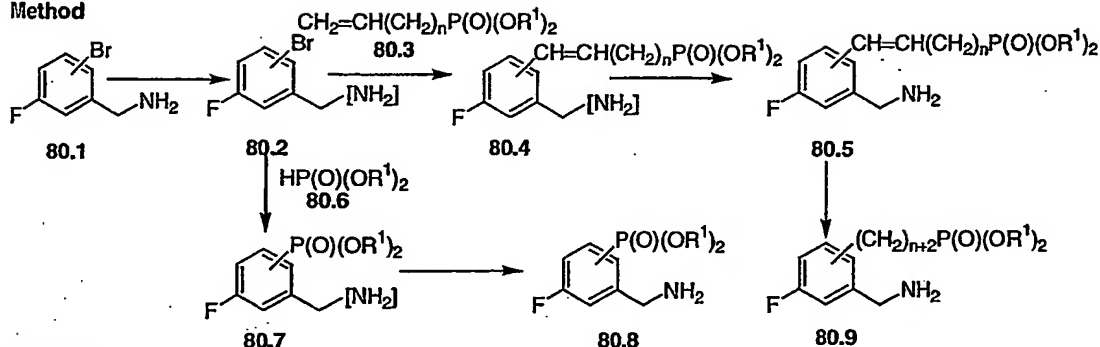


Example 2

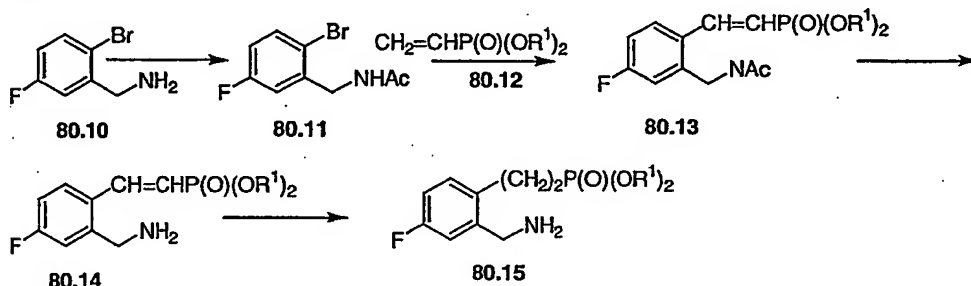


Scheme 80

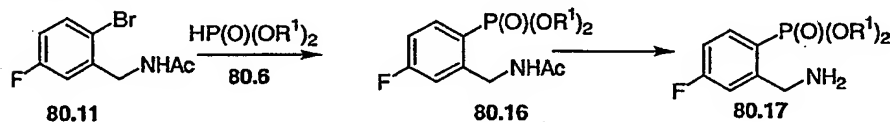
Method



Example 1



Example 2



Preparation of phosphonate-substituted fluorobenzylamines 39.4.

- 5 Schemes 81 and 82 illustrate the preparation of phosphonate-substituted 3-fluorobenzylamines 39.4 which are used in the preparation of the phosphonate esters 7.

Scheme 81 depicts the preparation of 3-fluorobenzylamines in which the phosphonate group is attached by means of an amide linkage. In this procedure, 3-fluorophenylalanine 81.1, (Alfa Aesar) is converted into the BOC derivative 81.2. The product is then coupled with a dialkyl aminoalkyl phosphonate 81.3 to afford the amide 81.4, which upon deprotection gives the amine 81.5.

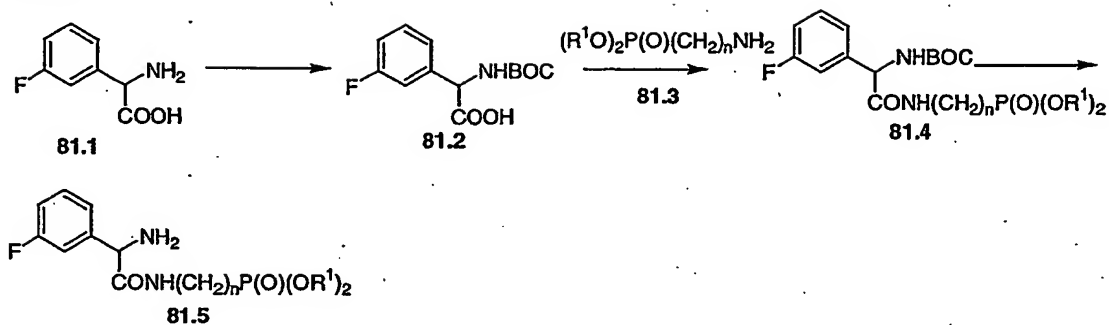
For example, the BOC-protected aminoacid 81.2 is coupled, in the presence of dicyclohexyl carbodiimide, with a dialkyl aminomethyl phosphonate 81.6 (Interchim), to prepare the amide 81.7. Deprotection then affords the amine 81.8.

Using the above procedures, but employing, in place of the amine 81.6 different amines 81.3, the corresponding products 81.5 are obtained.

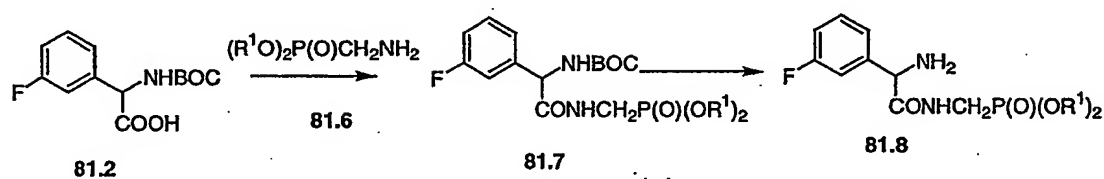
- Scheme 82 illustrates the preparation of fluorobenzylamine derivatives in which the
- 5 phosphonate group is attached by means of an alkyl or alkoxy chain. In this procedure, a hydroxyalkyl-substituted 3-fluorobenzylamine 82.1 is converted into the BOC derivative 82.2. This compound is then reacted with a dialkyl bromoalkyl phosphonate 82.3 to give the ether 82.4. The alkylation reaction is conducted in a polar organic solvent such as N-methylpyrrolidinone in the presence of a strong base such as sodium bis(trimethylsilyl)amide.
- 10 Deprotection of the product then affords the amine 82.5. Alternatively, the N-protected carbinol 82.2 is converted into the corresponding bromide 82.6, for example by reaction with N-bromoacetamide and triphenyl phosphine. The bromo compound is then reacted with a trialkyl phosphite in an Arbuzov reaction, as described above, to give the phosphonate 82.8, which upon deprotection affords the amine 82.9.
- 15 For example, 2-amino-2-(3-fluoro-phenyl)-ethanol 82.10, prepared as described in DE 4443892, is converted into the BOC derivative 82.11. The latter compound is then reacted in dimethylformamide at 100° with a dialkyl bromoethyl phosphonate 82.12 (Aldrich) and sodium hydride, to give the ether product 82.13. Removal of the BOC group then yields the amine 82.14.
- 20 Using the above procedures, but employing, in place of the carbinol 82.10 different carbinols 82.1, and/or different phosphonates 82.3 the corresponding products 82.5 are obtained. As a further example, the BOC-protected carbinol 82.11 is reacted with carbon tetrabromide and triphenylphosphine to produce the bromo compound 82.15. This material is heated at 120° with an excess of a trialkyl phosphite 82.7 to give the phosphonate 82.16. Deprotection then
- 25 yields the amine 82.17.
- Using the above procedures, but employing, in place of the carbinol 82.11 different carbinols 82.2, and/or different phosphonates 82.7 the corresponding products 82.9 are obtained.

Scheme 81

Method

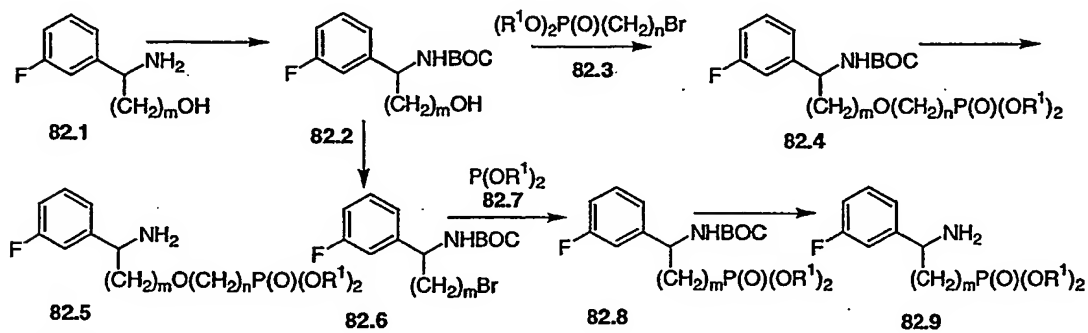


Example

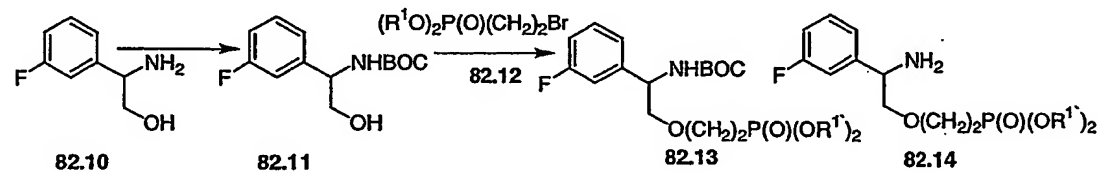


Scheme 82

Method



Example 1



5 Preparation of the phosphonate-containing tert. butanol derivatives 30.1.

Schemes 83 - 86 illustrate the preparation of the tert. butanol derivatives 30.1 which are employed in the preparation of the phosphonate esters 5.

Scheme 83 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an alkylene chain. In this procedure, a bromoalkyl carbinol 83.1 is reacted with a trialkyl phosphite 83.2 in an Arbuzov reaction, to afford the phosphonate 83.3.

5 For example, 4-bromo-2-methyl-butan-2-ol 83.4 prepared as described in Bioorg. Med. Chem. Lett., 2001, 9, 525, and a trialkyl phosphite 83.2 are heated at ca. 120° to produce the phosphonate 83.5.

Using the above procedures, but employing, in place of the bromo compound 83.4 different bromo compounds 83.1, and/or different phosphites 83.2 the corresponding products 83.3 are
10 obtained.

Scheme 84 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of an amide linkage. In this procedure, a carboxylic acid 84.1 is coupled with a dialkyl aminoalkyl phosphonate 84.2 to afford the amide 84.3. The reaction is
15 conducted under the conditions previously described (Scheme 1) for the preparation of amides.

For example, equimolar amounts of 3-hydroxy-3-methyl-butyric acid 84.4, (Fluka) and a dialkyl aminoethyl phosphonate 84.5, the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted in tetrahydrofuran in the presence of dicyclohexylcarbodiimide to
20 yield the amide 84.6.

Using the above procedures, but employing, in place of the carboxylic acid 84.4 different acids 84.1, and/or different amines 84.2 the corresponding products 84.3 are obtained.

Scheme 85 depicts the preparation of tert. butanol derivatives in which the phosphonate is
25 attached by means of a heteroatom and an alkylene chain. In this procedure, a hydroxy, mercapto or amino-substituted carbinol 85.1 is reacted with a dialkyl bromoalkyl phosphonate 85.2 to afford the ether, thioether or amine products 85.3. The reaction is conducted in a polar organic solvent in the presence of suitable base such as sodium hydride or cesium carbonate. For example, 4-mercapto-2-methyl-butan-2-ol 85.4 prepared as described in Bioorg. Med.
30 Chem. Lett., 1999, 9, 1715, is reacted in tetrahydrofuran containing cesium carbonate with a dialkyl bromobutyl phosphonate 85.5, the preparation of which is described in Synthesis, 1994, 9, 909, to yield the thioether 85.6.

Using the above procedures, but employing, in place of the thiol 85.4 different alcohols, thiol or amines 85.1, and/or different bromides 85.2 the corresponding products 85.3 are obtained.

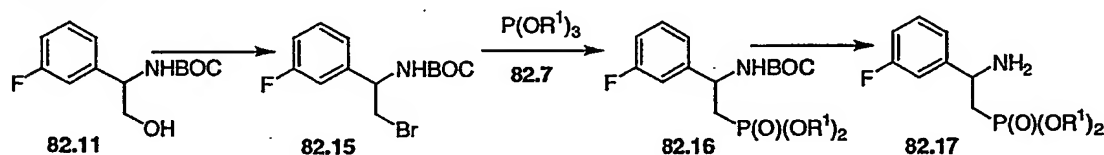
Scheme 86 depicts the preparation of tert. butanol derivatives in which the phosphonate is attached by means of a nitrogen and an alkylene chain. In this procedure, a hydroxyaldehyde 86.1 is reacted with a dialkyl aminoalkyl phosphonate 86.2 under reductive amination conditions, as described above, (Scheme 55) to afford the amine 86.3.

For example, 3-hydroxy-3-methyl-butyaldehyde 86.4 and a dialkyl aminoethyl phosphonate 86.5 the preparation of which is described in J. Org. Chem., 2000, 65, 676 are reacted together in the presence of sodium triacetoxyborohydride, to yield the amine 86.6.

Using the above procedures, but employing, in place of the aldehyde 86.4 different aldehydes 86.1, and/or different amines 86.2 the corresponding products 86.3 are obtained.

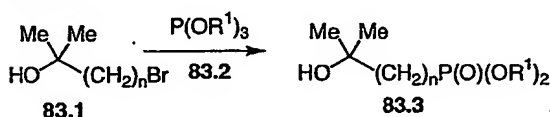
Scheme 82

Example 2

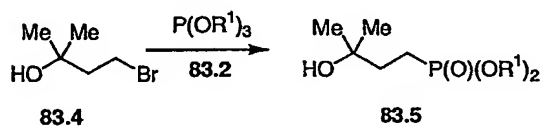


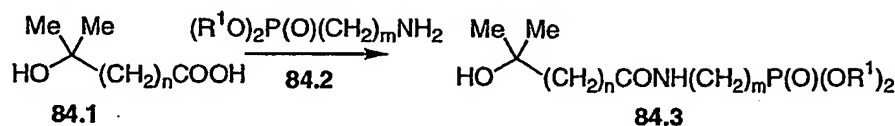
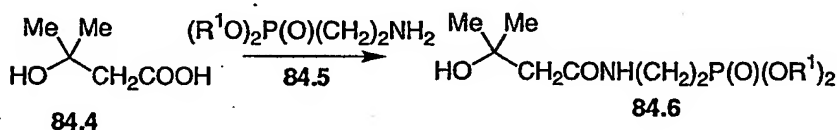
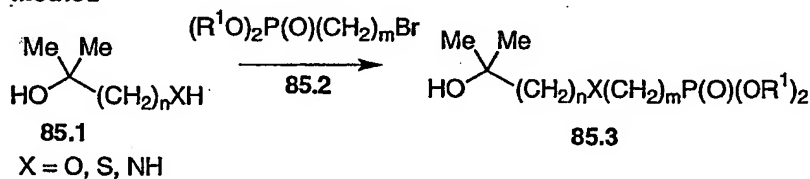
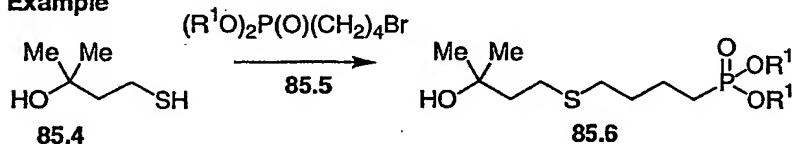
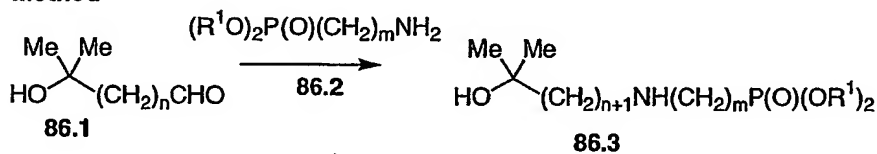
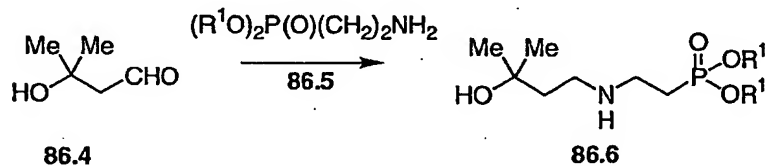
Scheme 83

Method



Example



Scheme 84**Method****Example****Scheme 85****Method****Example****Scheme 86****Method****Example****5 Preparation of the phosphonate-containing benzyl carbamates 43.4.**

Schemes 87 - 91 illustrate methods for the preparation of the benzyl carbamates 43.4 which are employed in the preparation of the phosphonate esters 9. The benzyl alcohols are obtained

by reduction of the corresponding benzaldehydes, the preparation of which is described in Schemes 87 - 90.

5 Scheme 87 illustrates the preparation of benzaldehyde phosphonates 87.3 in which the phosphonate group is attached by means of an alkylene chain incorporation a nitrogen atom. In this procedure, a benzene dialdehyde 87.1 is reacted with one molar equivalent of a dialkyl aminoalkyl phosphonate 87.2, under reductive amination conditions, as described above in Scheme 55, to yield the phosphonate product 87.3.

10 For example, benzene-1,3-dialdehyde 87.4 is reacted with a dialkyl aminopropyl phosphonate 87.5, (Acros) and sodium triacetoxyborohydride, to afford the product 87.6.

Using the above procedures, but employing, in place of benzene-1,3-dicarboxaldehyde 87.4, different benzene dialdehydes 87.1, and/or different phosphonates 87.2, the corresponding products 87.3 are obtained.

15 Scheme 88 illustrates the preparation of benzaldehyde phosphonates either directly attached to the benzene ring or attached by means of a saturated or unsaturated carbon chain. In this procedure, a bromobenzaldehyde 88.1 is coupled, as described above, with a dialkyl alkenylphosphonate 88.2, to afford the alkenyl phosphonate 88.3. Optionally, the product is reduced to afford the saturated phosphonate ester 88.4. Alternatively, the bromobenzaldehyde
20 is coupled, as described above, with a dialkyl phosphite 88.5 to afford the formylphenylphosphonate 88.6.

For example, as shown in Example 1, 3-bromobenzaldehyde 88.7 is coupled with a dialkyl propenylphosphonate 88.8 (Aldrich) to afford the propenyl product 88.9. Optionally, the product is reduced, for example by the use of diimide, to yield the propyl phosphonate 88.10.

25 Using the above procedures, but employing, in place of 3-bromobenzaldehyde 88.7, different bromobenzaldehydes 88.1, and/or different alkenyl phosphonates 88.2, the corresponding products 88.3 and 88.4 are obtained.

Alternatively, as shown in Example 2, 4-bromobenzaldehyde is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 88.5 to afford the 4-formylphenyl phosphonate
30 product 88.12.

Using the above procedures, but employing, in place of 4-bromobenzaldehyde 88.11, different bromobenzaldehydes 88.1, the corresponding products 88.6 are obtained.

Scheme 89 illustrates the preparation of formylphenyl phosphonates in which the phosphonate moiety is attached by means of alkylene chains incorporating two heteroatoms O, S or N. In this procedure, a formyl phenoxy, phenylthio or phenylamino alkanol, alkanethiol or alkylamine 89.1 is reacted with an equimolar amount of a dialkyl haloalkyl phosphonate 89.2, to afford the phenoxy, phenylthio or phenylamino phosphonate product 89.3. The alkylation reaction is effected in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base. The base employed depends on the nature of the nucleophile 89.1. In cases in which Y is O, a strong base such as sodium hydride or lithium hexamethyldisilazide is employed. In cases in which Y is S or N, a base such as cesium carbonate or dimethylaminopyridine is employed.

For example, 2-(4-formylphenylthio)ethanol 89.4, prepared as described in Macromolecules, 1991, 24, 1710, is reacted in acetonitrile at 60° with one molar equivalent of a dialkyl iodomethyl phosphonate 89.5, (Lancaster) to give the ether product 89.6.

Using the above procedures, but employing, in place of the carbinol 89.4, different carbinols, thiols or amines 89.1, and/or different haloalkyl phosphonates 89.2, the corresponding products 89.3 are obtained.

Scheme 90 illustrates the preparation of formylphenyl phosphonates in which the phosphonate group is linked to the benzene ring by means of an aromatic or heteroaromatic ring. In this procedure, a formylbenzeneboronic acid 90.1 is coupled, in the presence of a palladium catalyst, with one molar equivalent of a dibromoarene, 90.2, in which the group Ar is an aromatic or heteroaromatic group. The coupling of aryl boronates with aryl bromides to afford diaryl compounds is described in Palladium Reagents and Catalysts, by J. Tsuji, Wiley 1995, p. 218. The components are reacted in a polar solvent such as dimethylformamide in the presence of a palladium(0) catalyst and sodium bicarbonate. The product 90.3 is then coupled, as described above (Scheme 50) with a dialkyl phosphite 90.4 to afford the phosphonate 90.5.

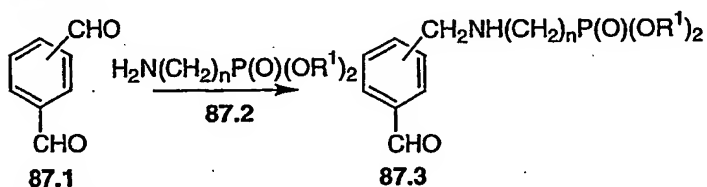
For example, 4-formylbenzeneboronic acid 90.6 is coupled with 2,5-dibromothiophene 90.7 to yield the phenylthiophene product 90.8. This compound is then coupled with the dialkyl phosphite 90.4 to afford the thienyl phosphonate 90.9.

Using the above procedures, but employing, in place of dibromothiophene **90.7**, different dibromoarenes **90.2**, and/or different formylphenyl boronates **90.1**, the corresponding products **90.5** are obtained.

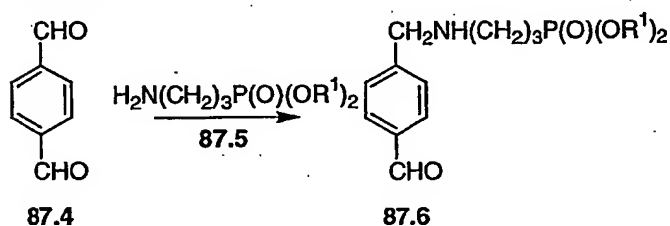
- 5 Scheme **91** illustrates the preparation of the benzyl carbamates **43.4** which are employed in the preparation of the phosphonate esters **9**. In this procedure, the substituted benzaldehydes **91.1**, prepared as shown in Schemes **87** – **90**, are converted into the corresponding benzyl alcohols **91.2**. The reduction of aldehydes to afford alcohols is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 527ff. The transformation is effected by the
- 10 use of reducing agents such as sodium borohydride, lithium aluminum tri-tertiarybutoxy hydride, diisobutyl aluminum hydride and the like. The resultant benzyl alcohol is then reacted with the aminoester **91.3** to afford the carbamate **91.4**. The reaction is performed under the conditions described below, Scheme **98**. For example, the benzyl alcohol is reacted with carbonyldiimidazole to produce an intermediate benzyloxycarbonyl imidazole, and the
- 15 intermediate is reacted with the aminoester **91.3** to afford the carbamate **91.4**. The methyl ester is then hydrolyzed to yield the carboxylic acid **43.4**.

Scheme 87

Method

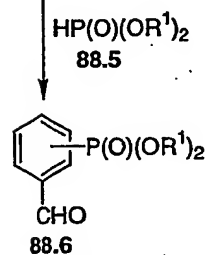
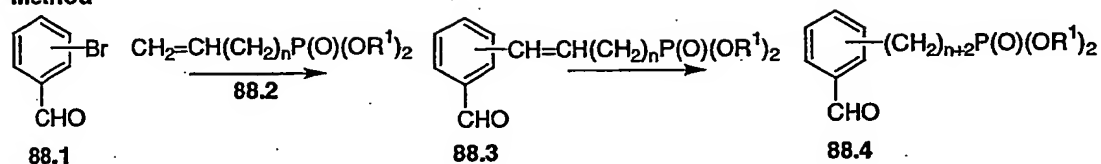


Example

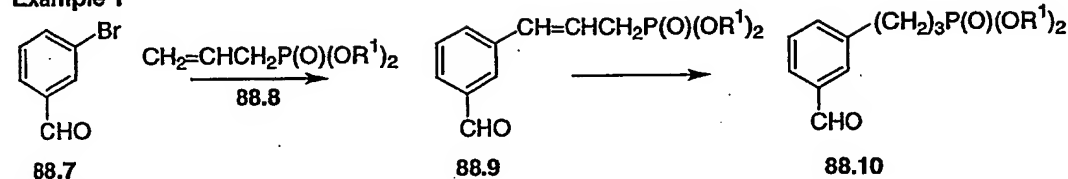


Scheme 88

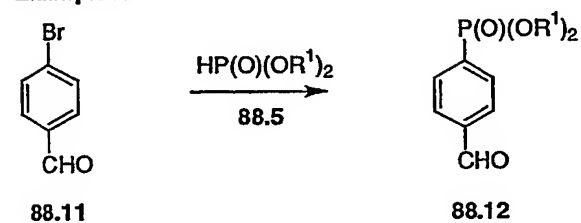
Method



Example 1

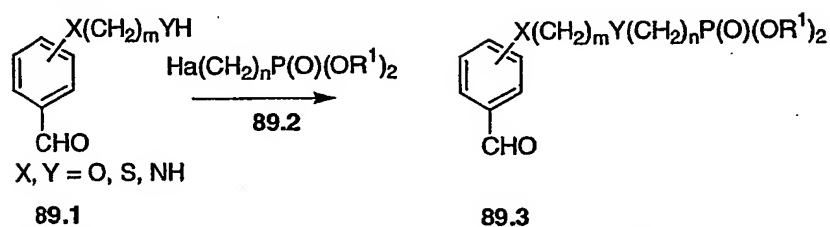


Example 2

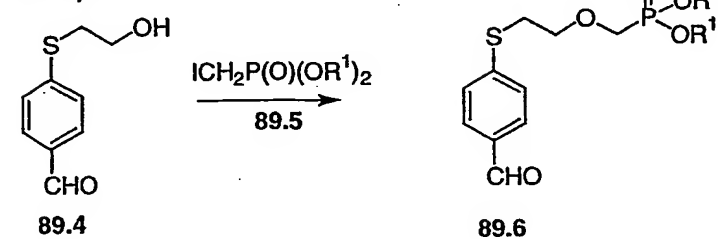


Scheme 89

Method

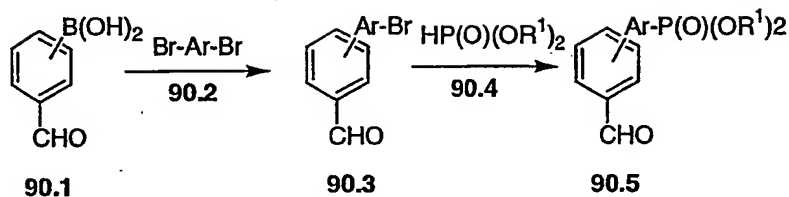


Example

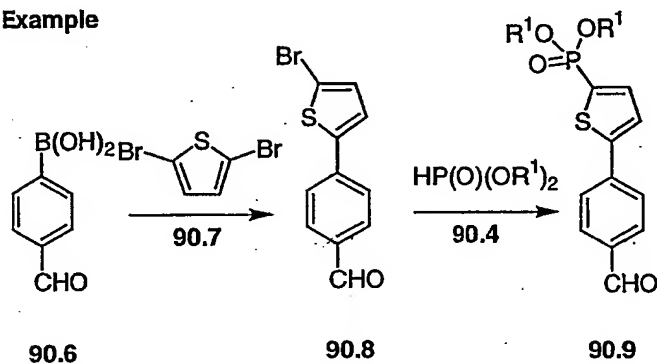


Scheme 90

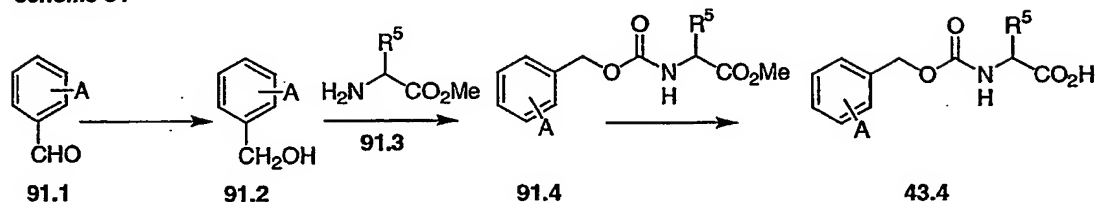
Method



Example



Scheme 91



5

Preparation of phosphonate-containing benzenesulfonyl chlorides 20.2.

Schemes 92 - 97 illustrate methods for the preparation of the sulfonyl chlorides 20.2 which are employed in the preparation of the phosphonate esters 4. Sulfonic acids and/or sulfonyl halides are obtained by oxidation of the corresponding thiols, as described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 813, and in Tet. 1965, 21, 2271. For example, the phosphonate-containing thiols which are prepared according to Schemes 63 - 72 are transformed into the corresponding sulfonic acids by oxidation with bromine in aqueous organic solution, as described in J. Am. Chem. Soc., 59, 811, 1937, or by oxidation with hydrogen peroxide, as described in Rec. Trav. Chim., 54, 205, 1935, or by reaction with

15

oxygen in alkaline solution, as described in Tet. Let., 1963, 1131, or by the use of potassium superoxide, as described in Aust. J. Chem., 1984, 37, 2231. Schemes 92- 96 describe the preparation of phosphonate-substituted benzenesulfonic acids; Scheme 97 describes the conversion of the sulfonic acids into the corresponding sulfonyl chlorides. Alternatively, the intermediate thiols, when produced, can be directly converted to the sulfonyl chloride as described in Scheme 97a

Scheme 92 depicts the preparation of variously substituted benzenesulfonic acids in which the phosphonate group is directly attached to the benzene ring. In this procedure, a bromo-substituted benzenethiol 92.1 is protected, as previously described. The protected product 92.2 is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite 92.3, to give the corresponding phosphonate 92.4. The thiol group is then deprotected to afford the thiol 92.5, and this compound is oxidized to afford the sulfonic acid 92.6.

For example, 4-bromobenzenethiol 92.7 is converted into the S-adamantyl derivative 92.8, by reaction with 1-adamantanol in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978. The product is then reacted with a dialkyl phosphite and a palladium catalyst, as described previously, to yield the phosphonate 92.9. The adamantyl group is then removed by reaction with mercuric acetate in trifluoroacetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978, to give the thiol 92.10. The product is then reacted with bromine in aqueous solution to prepare the sulfonic acid 92.11.

Using the above procedures, but employing, in place of the thiol 92.7, different thiols 92.1, and/or different dialkyl phosphites 92.3, the corresponding products 92.6 are obtained.

Scheme 93 illustrates the preparation of amino-substituted benzenesulfonic acids in which the phosphonate group is attached by means of an alkoxy group. In this procedure, a hydroxy amino-substituted benzenesulfonic acid 93.1 is reacted with a dialkyl bromoalkyl phosphonate 93.2 to afford the ether 93.3. The reaction is performed in a polar solvent such as dimethylformamide in the presence of a base such as potassium carbonate. The yield of the product 93.3 is increased by treatment of the crude reaction product with dilute aqueous base, so as to hydrolyze any sulfonic esters which are produced.

For example, 3-amino-4-hydroxybenzenesulfonic acid 93.4 (Fluka) is reacted with a dialkyl bromopropyl phosphonate 93.5 prepared as described in J. Am. Chem. Soc., 2000, 122, 1554,

in dimethylformamide containing potassium carbonate, followed by the addition of water, to produce the ether 93.6.

Using the above procedures, but employing, in place of the phenol 93.4, different phenols 93.1, and/or different phosphonates 93.2, the corresponding products 93.3 are obtained.

5

Scheme 94 illustrates the preparation of methoxyl-substituted benzenesulfonic acids in which the phosphonate group is attached by means of an amide group. In this procedure, a methoxy amino-substituted benzenesulfonic acid 94.1 is reacted, as described previously for the preparation of amides, with a dialkyl carboxyalkyl phosphonate 94.2 to produce the amide 94.3.

10

For example, 3-amino-4-methoxybenzenesulfonic acid 94.4, (Acros) is reacted in dimethylformamide solution with a dialkyl phosphonoacetic acid 94.2 (Aldrich) and dicyclohexyl carbodiimide, to produce the amide 94.6.

15

Using the above procedures, but employing, in place of the amine 94.4, different amines 94.1, and/or different phosphonates 94.2, the corresponding products 94.3 are obtained.

20

Scheme 95 illustrates the preparation of substituted benzenesulfonic acids in which the phosphonate group is attached by means of a saturated or unsaturated alkylene group. In this procedure, a halo-substituted benzenesulfonic acid 95.1 is coupled, in a palladium catalyzed Heck reaction with a dialkyl alkenyl phosphonate 95.2 to afford the phosphonate 95.3. Optionally, the product is reduced, for example by catalytic hydrogenation over a palladium catalyst, to give the saturated analog 95.4.

25

For example, 4-amino-3-chlorobenzenesulfonic acid 95.5 (Acros) is reacted in N-methylpyrrolidinone solution at 80° with a dialkyl vinylphosphonate 95.6 (Aldrich), palladium (II) chloride bis(acetonitrile), sodium acetate and tetraphenylphosphonium chloride, as described in Ang. Chem. Int. Ed. Engl., 37, 481, 1998, to produce the olefinic product 95.7. Catalytic hydrogenation using a 5% palladium on carbon catalyst then affords the saturated analog 95.8.

30

Using the above procedures, but employing, in place of the chloro compound 95.5, different chlorides 95.1, and/or different phosphonates 95.2, the corresponding products 95.3 and 95.4 are obtained.

Scheme 96 depicts the preparation of benzenesulfonic acids in which the phosphonate group is attached by means of an amide linkage. In this procedure, an amino carboxy substituted benzene thiol 96.1 is coupled with a dialkyl aminoalkyl phosphonate 96.2 to produce the amide 96.3. The product is then oxidized, as described above, to afford the corresponding sulfonic acid 96.4.

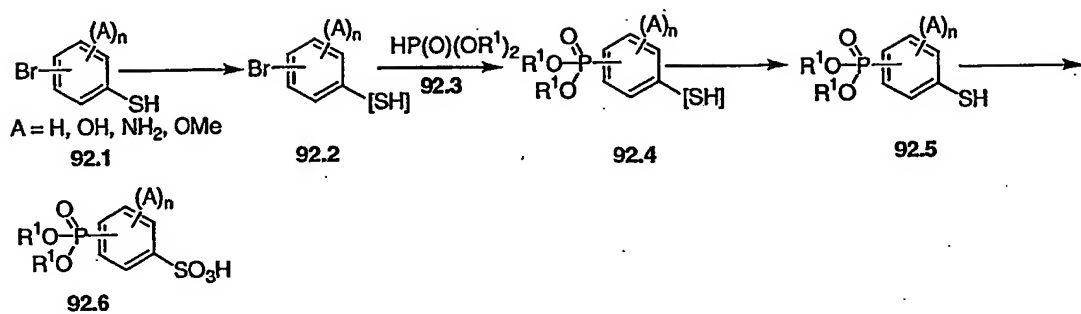
- For example, 2-amino-5-mercaptopbenzoic acid 96.5, prepared as described in Pharmazie, 1973, 28, 433, is reacted with a dialkyl aminoethyl phosphonate 96.6 and dicyclohexyl carbodiimide, to prepare the amide 96.7. The product is then oxidized with aqueous hydrogen peroxide to yield the sulfonic acid 96.8.
- Using the above procedures, but employing, in place of the carboxylic acid 96.5, different acids 96.1, and/or different phosphonates 96.2, the corresponding products 96.4 are obtained.

- Scheme 97 illustrates the conversion of benzenesulfonic acids into the corresponding sulfonyl chlorides. The conversion of sulfonic acids into sulfonyl chlorides is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 821. The transformation is effected by the use of reagents such as thionyl chloride or phosphorus pentachloride.
- For example, as shown in Scheme 97, the variously substituted phosphonate-containing benzenesulfonic acids 97.1, prepared as described above, are treated with thionyl chloride, oxalyl chloride, phosphorus pentachloride, phosphorus oxychloride and the like to prepare the corresponding sulfonyl chlorides 97.2.

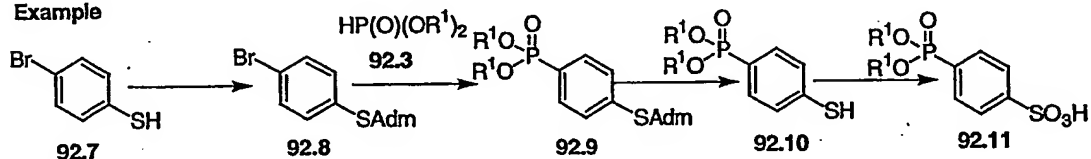
- Scheme 97a illustrates the conversion of thiols into the corresponding sulfonyl chlorides which can be applied to any of the thiol intermediates in Schemes 92-96. The thiol is oxidized as described in Synthesis 1987, 4, 409 or J. Med. Chem. 1980, 12, 1376 to afford the sulfonyl chloride directly. For example, treatment of protected thiol 97a.1, prepared from 96.7 using standard protecting groups for amines as described in Greene and Wuts, third edition, ch 7, with HCl and chlorine affords the sulfonyl chloride 97a.2. Alternatively treatment of 92.10 with the same conditions gives the sulfonyl chloride 97a.3.

Scheme 92

Method

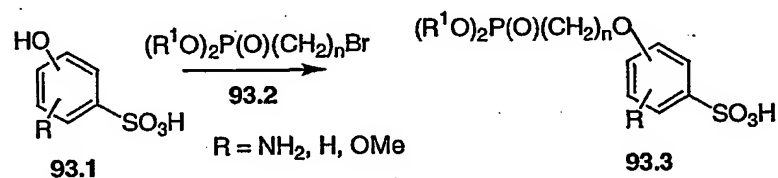


Example

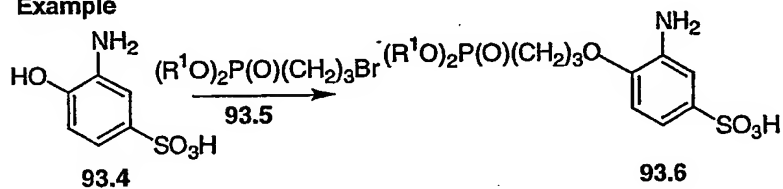


Scheme 93

Method

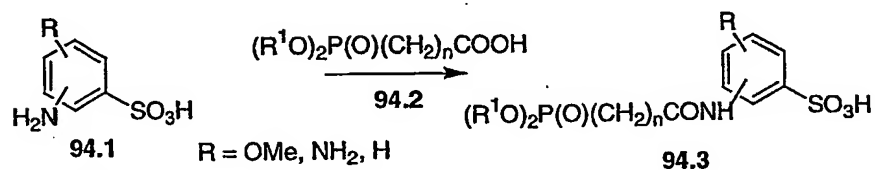


Example

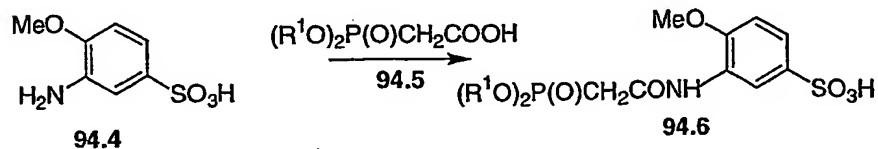


Scheme 94

Method

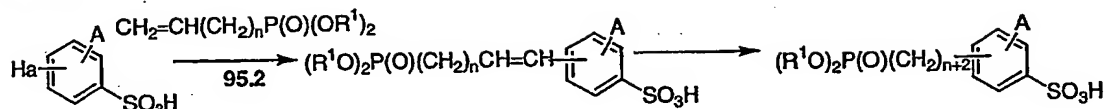


Example



Scheme 95

Method

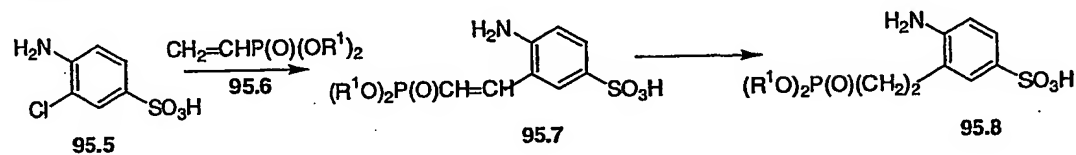


A = H, OMe, NH₂
95.1

95.3

95.4

Example



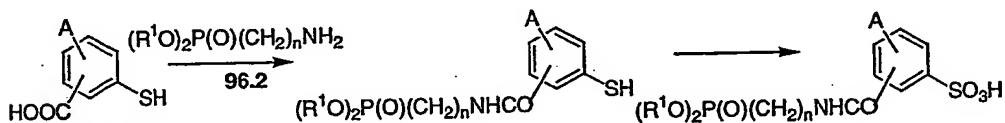
95.5

95.7

95.8

Scheme 96

Method

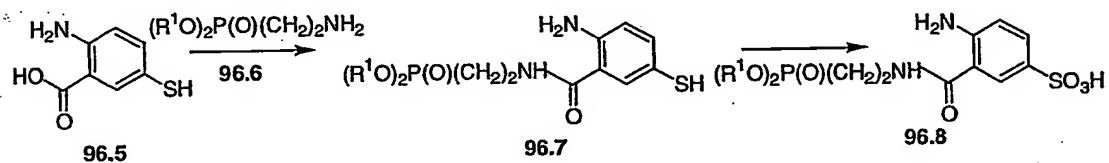


A = H, OMe, Ha
96.1

96.3

96.4

Example

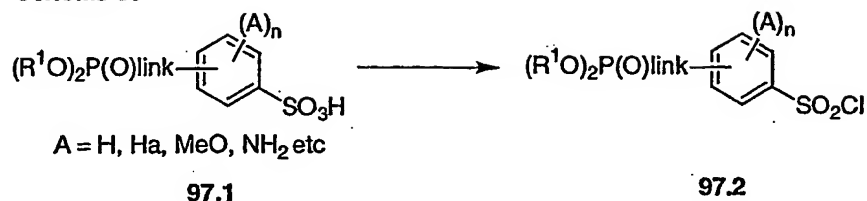


96.5

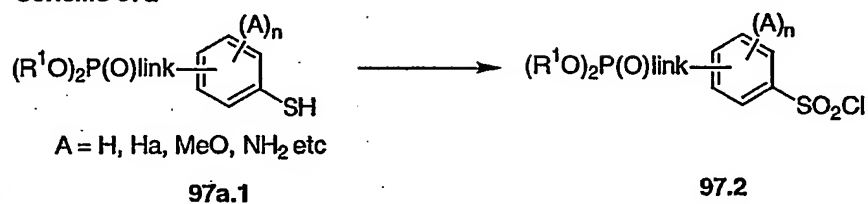
96.7

96.8

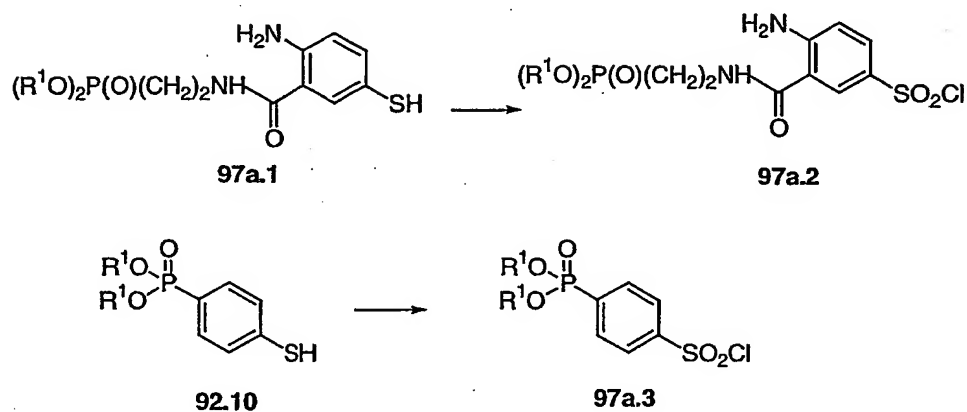
Scheme 97



Scheme 97a



Example



5 Preparation of carbamates.

The phosphonate esters 1 - 4 in which R^4 is formally derived from the carboxylic acids shown in Chart 5c, and the phosphonate esters 5 and 9 contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A.

- 10 R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.

Scheme 98 illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme 98, in the general reaction generating carbamates, a carbinol 98.1, is converted into the activated derivative 98.2 in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described below. The activated derivative 98.2 is then
5 reacted with an amine 98.3, to afford the carbamate product 98.4. Examples 1 - 7 in Scheme 98 depict methods by which the general reaction is effected. Examples 8 - 10 illustrate alternative methods for the preparation of carbamates.

Scheme 98, Example 1 illustrates the preparation of carbamates employing a chloroformyl derivative of the carbinol 98.1. In this procedure, the carbinol is reacted with phosgene, in an
10 inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 98.6. The latter compound is then reacted with the amine component 98.3, in the presence of an organic or inorganic base, to afford the carbamate 98.7. For example, the chloroformyl compound 98.6 is reacted with the amine 98.3
15 in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate 98.7. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme 98, Example 2 depicts the reaction of the chloroformate compound 98.6 with
20 imidazole to produce the imidazolide 98.8. The imidazolide product is then reacted with the amine 98.3 to yield the carbamate 98.7. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 98 Example 3, depicts the reaction of the chloroformate 98.6 with an activated
25 hydroxyl compound R"OH, to yield the mixed carbonate ester 98.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 98.19 - 98.24 shown in Scheme 98, and similar compounds. For
30 example, if the component R"OH is hydroxybenztriazole 98.19, N-hydroxysuccinimide 98.20, or pentachlorophenol, 98.21, the mixed carbonate 98.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of

dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 98.22 or 2-hydroxypyridine 98.23 is performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

5 Scheme 98 Example 4 illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole 98.8 is employed. In this procedure, a carbinol 98.5 is reacted with an equimolar amount of carbonyl diimidazole 98.11 to prepare the intermediate 98.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 98.8 is then reacted with an equimolar amount of the
10 amine R'NH₂ to afford the carbamate 98.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 98.7.

Scheme 98, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxy carbonyl benzotriazole 98.13. In this procedure, a carbinol ROH is reacted at ambient
15 temperature with an equimolar amount of benzotriazole carbonyl chloride 98.12, to afford the alkoxy carbonyl product 98.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine R'NH₂ to afford the carbamate 98.7. The reaction is conducted in toluene or ethanol, at from ambient temperature
20 to about 80° as described in Syn., 1977, 704.

Scheme 98, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 98.14, is reacted with a carbinol 98.5 to afford the intermediate alkyloxycarbonyl intermediate 98.15. The latter reagent is then reacted with the amine R'NH₂ to afford the carbamate 98.7. The procedure in which the reagent 98.15 is derived from
25 hydroxybenzotriazole 98.19 is described in Synthesis, 1993, 908; the procedure in which the reagent 98.15 is derived from N-hydroxysuccinimide 98.20 is described in Tet. Lett., 1992, 2781; the procedure in which the reagent 98.15 is derived from 2-hydroxypyridine 98.23 is described in Tet. Lett., 1991, 4251; the procedure in which the reagent 98.15 is derived from 4-nitrophenol 98.24 is described in Syn. 1993, 199. The reaction between equimolar amounts
30 of the carbinol ROH and the carbonate 98.14 is conducted in an inert organic solvent at ambient temperature.

Scheme 98, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides 98.16. In this procedure, an alkyl chloroformate 98.6 is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide 98.16. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate 98.7. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

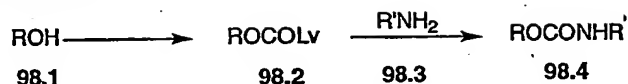
Scheme 98, Example 8 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine 98.17. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate 98.7.

Scheme 98, Example 9 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate 98.18. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate 98.7.

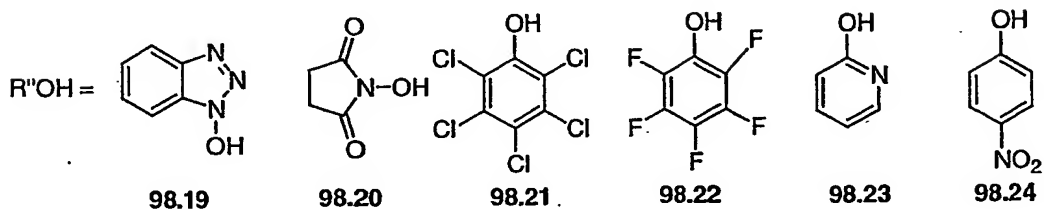
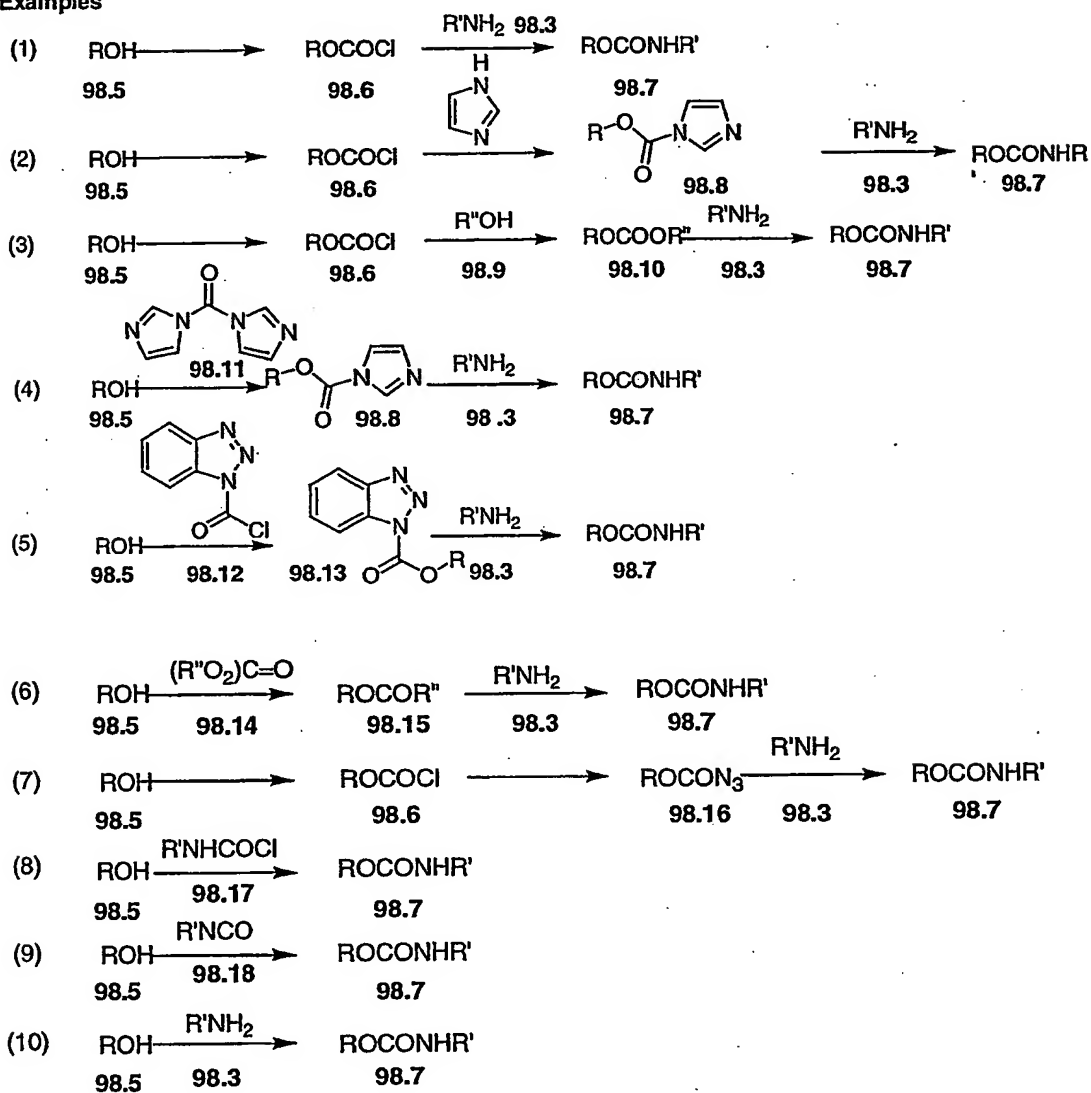
Scheme 98, Example 10 illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine $R'NH_2$. In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate 98.7.

Scheme 98

General reaction



Examples



Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 97 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Charts 1 and 2, may be the same or different. The R¹ groups attached to the phosphonate esters 1 - 13, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 99. The group R in Scheme 99 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1 - 13 or in precursors thereto. The R¹ group may be changed, using the procedures described below, either in the precursor compounds, or in the esters 1 - 13. The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 99.1 into the corresponding phosphonate monoester 99.2 (Scheme 99, Reaction 1) is accomplished by a number of methods. For example, the ester 99.1 in which R¹ is an aralkyl group such as benzyl, is converted into the monoester compound 99.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110°. The conversion of the diester 99.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 99.2 is effected by treatment of the ester 99.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran.

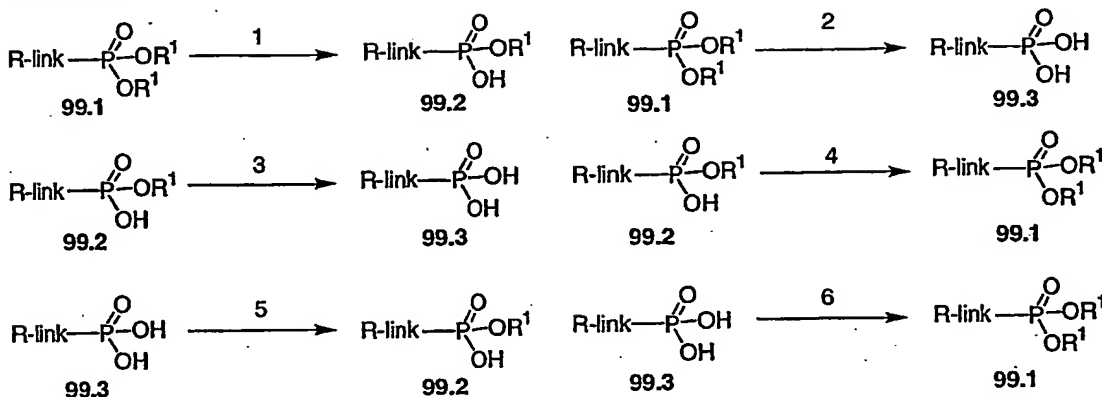
Phosphonate diesters 99.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, are converted into the monoesters 99.2 in which R¹ is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, are converted into the monoester 99.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **99.1** or a phosphonate monoester **99.2** into the corresponding phosphonic acid **99.3** (Scheme **99**, Reactions **2** and **3**) is effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **99.2** in which R¹ is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **99.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **99.2** in which R¹ is alkenyl such as, for example, allyl, is converted into the phosphonic acid **99.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **99.1** in which R¹ is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **99.1** in which R¹ is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **99.2** into a phosphonate diester **99.1** (Scheme **99**, Reaction **4**) in which the newly introduced R¹ group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **99.2** is reacted with a hydroxy compound R¹OH, in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **99.2** to the diester **99.1** is effected by the use of the Mitsunobu reaction, as described above, Scheme **49**. The substrate is reacted with the hydroxy compound R¹OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **99.2** is transformed into the phosphonate diester **99.1**, in which the introduced R¹ group is alkenyl or aralkyl, by reaction of the monoester with the halide R¹Br, in

- which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **99.2** is
- 5 transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as triethylamine, to afford the phosphonate diester **99.1**.
- 10 A phosphonic acid $R\text{-link-P}(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme 99, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **99.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.
- A phosphonic acid $R\text{-link-P}(O)(OH)_2$ **99.3** is transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **99.1** (Scheme 99, Reaction 6) by a coupling reaction with the hydroxy compound
- 15 R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine.
- Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters **99.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in
- 20 pyridine at ca 70° . Alternatively, phosphonic acids **99.3** are transformed into phosphonic esters **99.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **99.1**.

Scheme 99



General applicability of methods for introduction of phosphonate substituents.

The procedures described for the introduction of phosphonate moieties (Schemes 47 - 97) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids, (Schemes 47 - 51) are applicable to the introduction of phosphonate moieties into quinolines, thiophenols, isobutylamines, cyclopentylamines, tert. butanols, benzyl alcohols, phenylalanines, benzylamines and benzenesulfonic acids, and the methods described for the introduction of phosphonate moieties into the above-named substrates (Schemes 52 - 97) are applicable to the introduction of phosphonate moieties into hydroxymethyl benzoic acid substrates.

Preparation of phosphonate intermediates 11 - 13 with phosphonate moieties incorporated into the R², R³ or R⁴ groups.

15

The chemical transformations described in Schemes 1 - 99 illustrate the preparation of compounds 1 - 10 in which the phosphonate ester moiety is attached to the substructures listed above. The various chemical methods employed for the introduction of phosphonate ester groups into the above-named moieties can, with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds R⁴COOH, R³Cl, R²NH₂. The resultant phosphonate-containing analogs, designated as R^{4a}COOH, R^{3a}Cl and NH₂R^{2a} are then, using the procedures described above, employed in the preparation of the compounds 11, 12 and 13. The procedures required for the

20

utilization of the phosphonate-containing analogs are the same as those described above for the utilization of the compounds R^2NH_2 , R^3Cl and R^4COOH .

5 KNI-like phosphonate protease inhibitors (KNILPPI)

Preparation of the intermediate phosphonate esters 1-12.

The structures of the intermediate phosphonate esters 1 to 12 and the structures for the component groups R^1 , R^2 , R^3 , R^7 , R^9 , X and Y of this invention are shown in Charts 1 and 2.

10 The structures of the R^8COOH components are shown in Charts 3a, 3b and 3c.

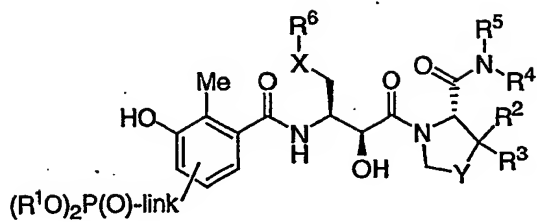
The structures of the $R^{10}R^{11}NH$ and R^4R^5NH components are shown in Charts 4a, and 4b respectively. The structures of the R^6XCH_2 groups are shown in Chart 5. Specific stereoisomers of some of the structures are shown in Charts 1 - 5; however, all stereoisomers are utilized in the syntheses of the compounds 1 to 12. Subsequent chemical modifications to
15 the compounds 1 to 12, as described herein, permit the synthesis of the final compounds of this invention.

The intermediate compounds 1 to 12 incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. Charts 6 and 7 illustrate examples of the linking groups present in the
20 structures 1 - 12.

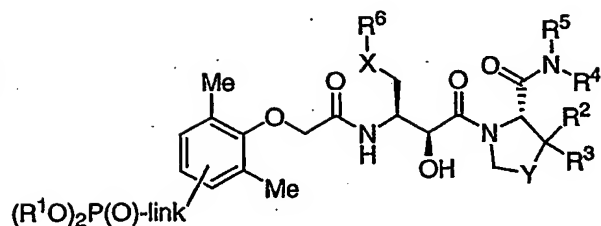
Schemes 1 - 103 illustrate the syntheses of the intermediate phosphonate compounds of this invention, 1 - 10, and of the intermediate compounds necessary for their synthesis. The preparation of the phosphonate esters 11 and 12, in which the phosphonate moiety is incorporated into the groups R^8COOH and $R^{10}R^{11}NH$, is also described below.

25

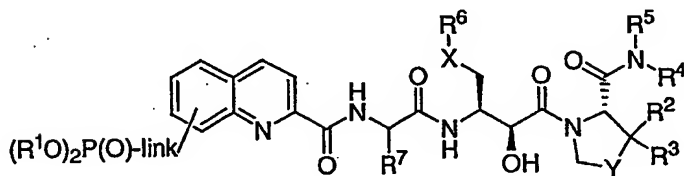
Chart 1



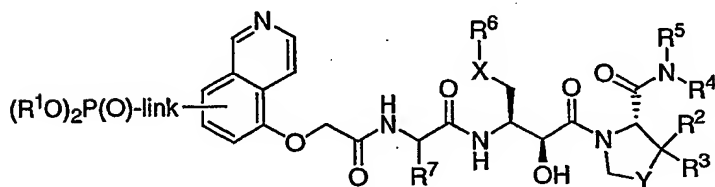
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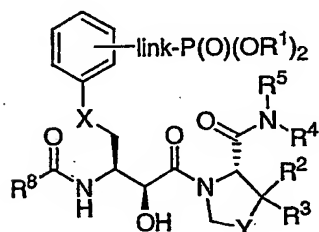
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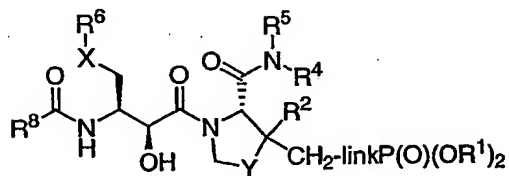
3



4



5



6

R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl

R^2, R^3 = H, H; H, methyl; methyl, methyl; H, Cl

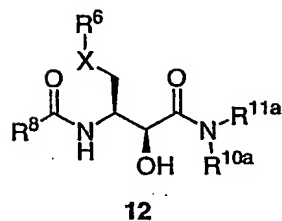
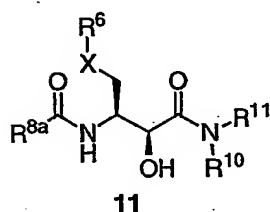
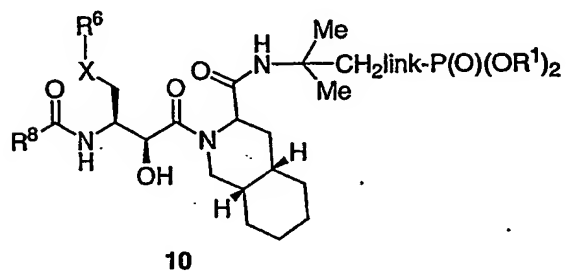
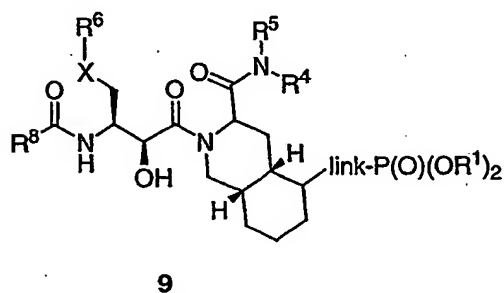
R^7 = alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $CH_2NHCOCF_3$

X = S or direct bond

Y = S, CH_2

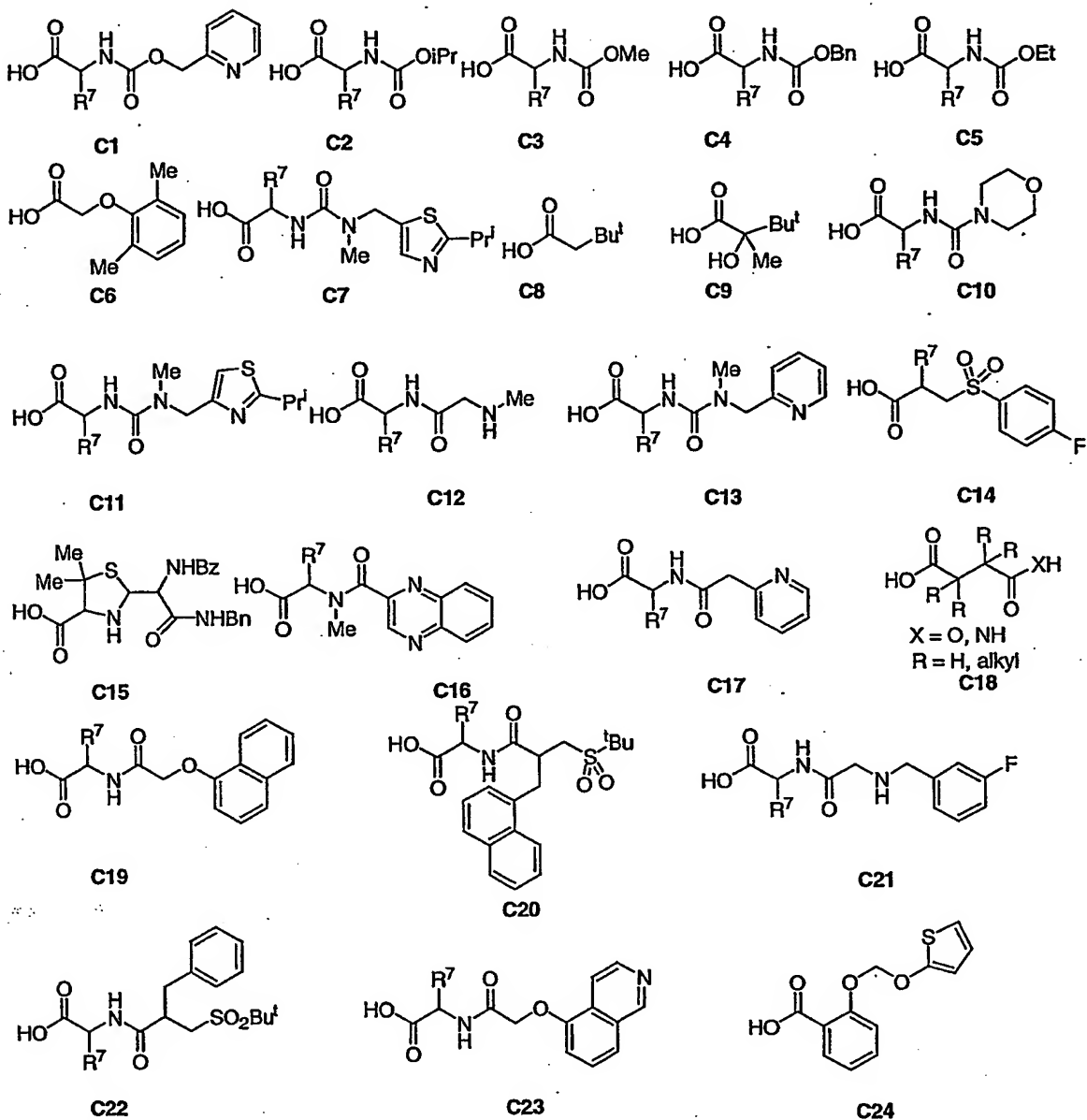
$$\begin{array}{c}
 \text{R}^6 \\
 | \\
 \text{X} \\
 | \\
 \text{C(=O)NH} \text{---} \text{CH} \text{---} \text{CH} \text{---} \text{C(=O)N} \text{---} \text{C} \text{---} \text{C} \text{---} \text{C} \text{---} \text{CH}_2 \text{link-P(O)(OR}^1\text{)}_2 \\
 | \quad | \quad | \quad | \quad | \quad | \quad | \quad | \\
 \text{R}^8 \quad \text{H} \quad \text{OH} \quad \text{O} \quad \text{H} \quad \text{Me} \quad \text{Me} \quad \text{R}^2 \quad \text{R}^3 \quad \text{Y}
 \end{array}$$

7

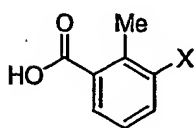


R^{10a}, R^{11a} = phosphonate-containing R^{10} or R^{11}

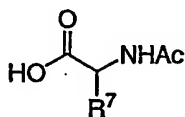
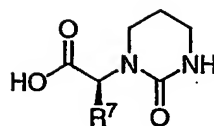
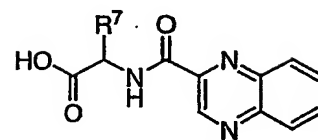
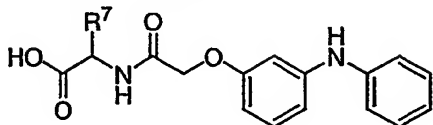
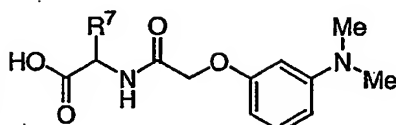
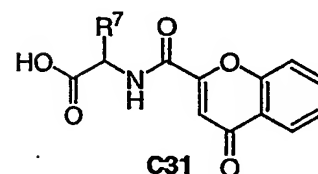
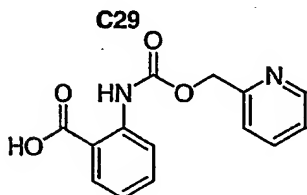
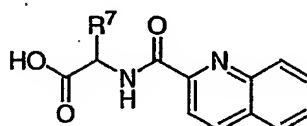
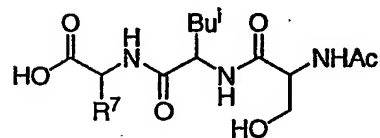
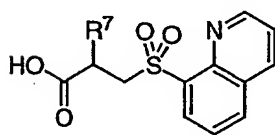
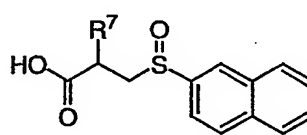
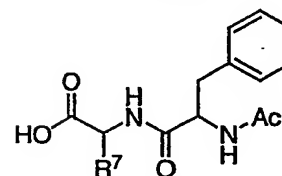
$R^1 = \text{H, alkyl, haloalkyl, alkenyl, aralkyl, aryl}$
 $R^2, R^3 = \text{H, H; H, methyl; methyl, methyl; H, Cl.}$
 $R^9 = \text{H, methyl}$
 $X = \text{S or direct bond}$
 $Y = \text{S, CH}_2$

Chart 3a Structures of the R⁸COOH components

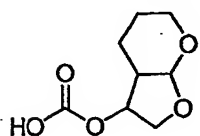
R⁷ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc,
 CH₂NHCOCF₃

Chart 3b Structures of the R⁷COOH components

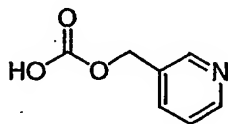
C25
X = OH, NH₂

**C26****C27****C28****C29****C30****C31****C32****C33****C34****C35****C36****C37**

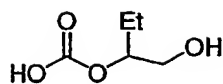
R⁷ = alkyl, CH₂SO₂CH₃, C(CH₃)₂SO₂CH₃, CH₂CONH₂, CH₂SCH₃, imidaz-4-ylmethyl, CH₂NHAc, CH₂NHCOCF₃

Chart 3c Structures of the R⁸COOH components

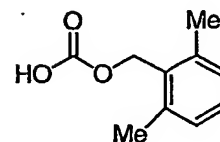
C38



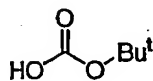
C39



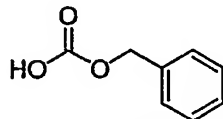
C40



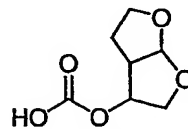
C41



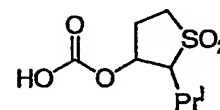
C42



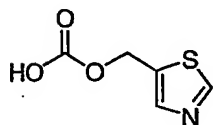
C43



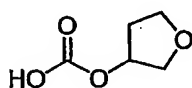
C44



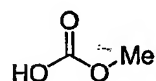
C45



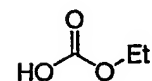
C46



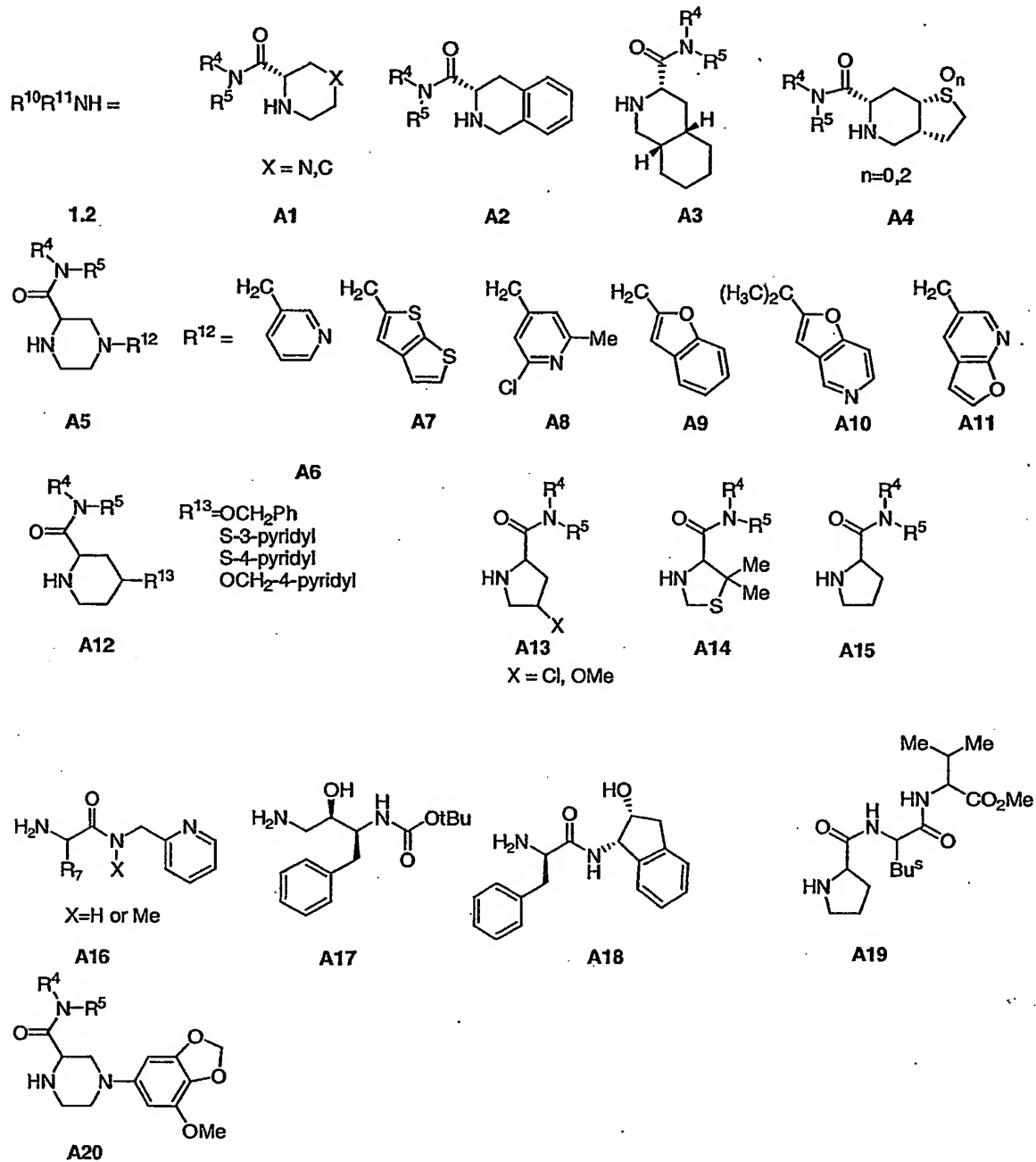
C47



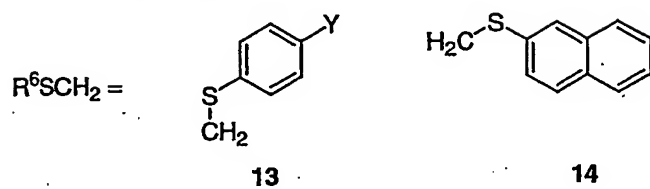
C48



C49

Chart 4a Structures of the $R^{10}R^{11}NH$ components

$R^7 =$ alkyl, $CH_2SO_2CH_3$, $C(CH_3)_2SO_2CH_3$, CH_2CONH_2 , CH_2SCH_3 , imidaz-4-ylmethyl, CH_2NHAc , $CH_2NHCOCF_3$

Chart 5 Structures of the R^6XCH_2 groups.

Y = H, F

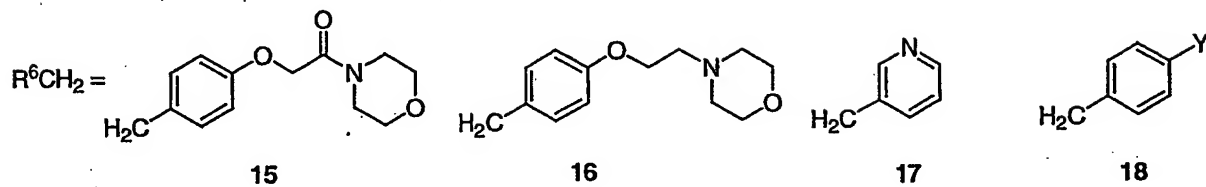
Y = H, OC_2H_5 , $OCH_2C_6H_5$

Chart 6 Examples of the linking groups between the scaffold and the phosphonate moiety.

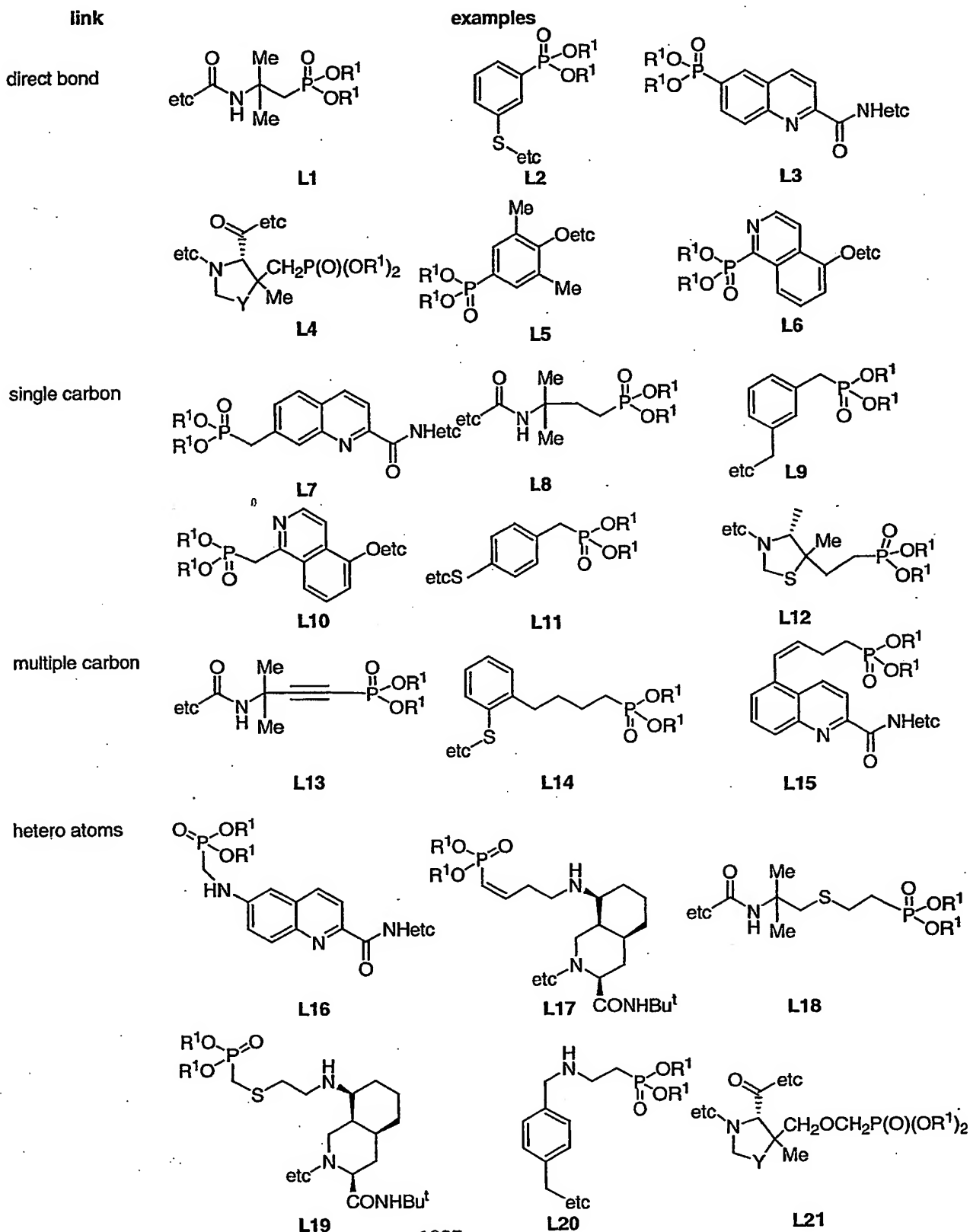
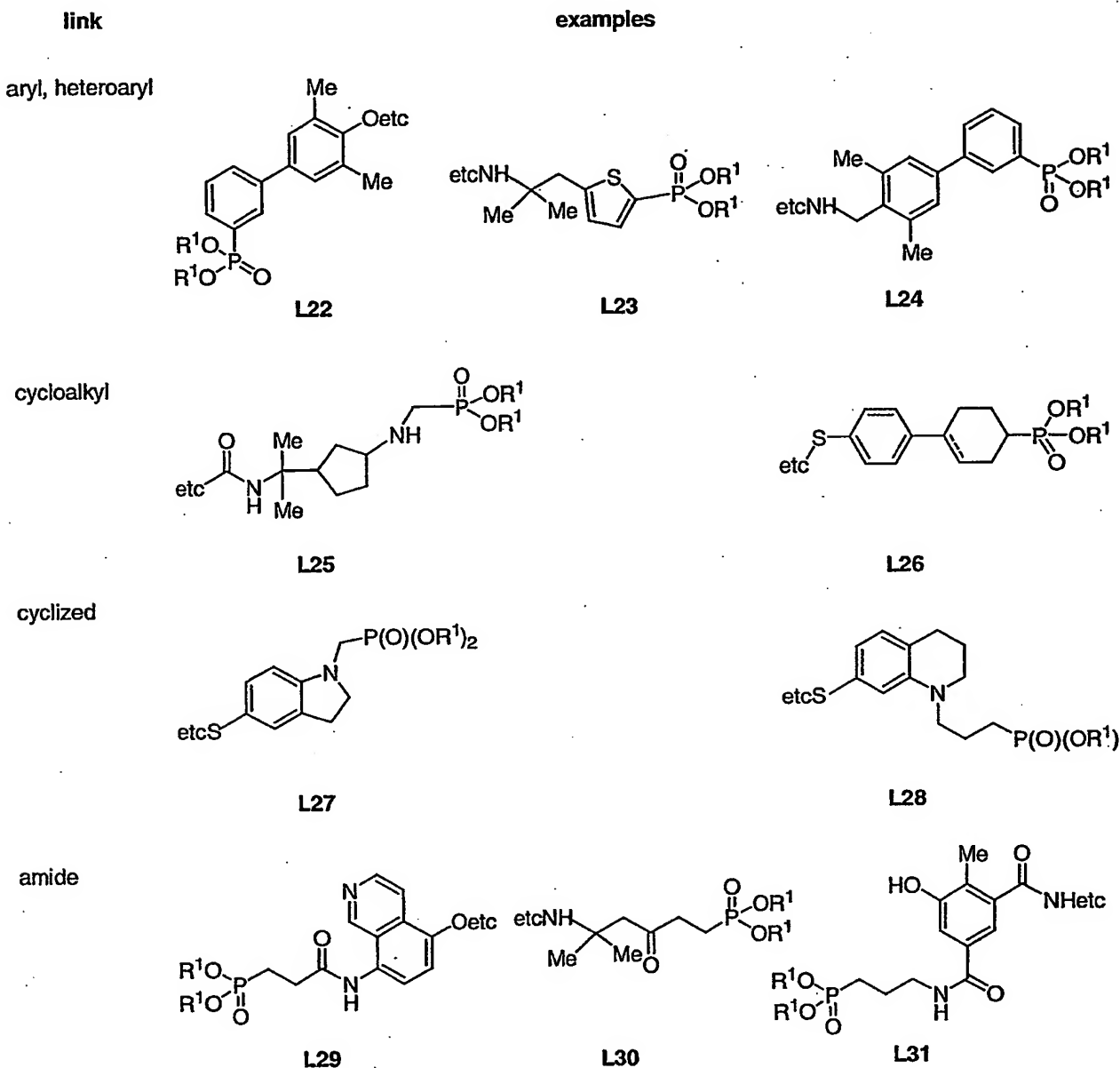


Chart 7 Examples of the linking groups between the scaffold and the phosphonate moiety.**Protection of reactive substituents.**

5

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the

art. Protection and deprotection of functional groups are described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], etc.

5

Preparation of the phosphonate ester intermediates 1 in which X is a direct bond.

Schemes 1 and 2 illustrate the preparation of the phosphonate esters 1 in which X is a direct bond. As shown in Scheme 1, a BOC-protected cyclic aminoacid 1.1 is reacted with an amine 1.2 to afford the amide 1.3. The carboxylic acid 1.1 in which Y is CH₂ and R² and R³ are H is commercially available (Bachem). The preparation of the carboxylic acid 1.1 in which Y is S and R² and R³ are CH₃ is described in Tet. Asym., 13, 2002, 1201; the preparation of the carboxylic acid 1.1 in which Y is S and R² is H and R³ is CH₃ is described in JP 60190795; the preparation of the carboxylic acid 1.1 in which Y is S and R² and R³ are H is described in EP 0574135; the preparation of the carboxylic acid 1.1 in which Y is CH₂, R² is H and R³ is Cl is described in EP 587311.

The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide. Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. Preferably, equimolar amounts of the carboxylic acid 1.1 and the amine 1.2 are reacted together in tetrahydrofuran solution in the presence of

dicyclohexylcarbodiimide and N-hydroxysuccinimide, for example as described in EP 574135, to yield the amide product 1.3. The BOC protecting group is then removed to give the free amine 1.4. The removal of BOC protecting groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 328. The deprotection can be effected by treatment of the BOC compound with anhydrous acids, for example, hydrogen chloride or trifluoroacetic acid, or by reaction with trimethylsilyl iodide or aluminum chloride. Preferably, the BOC protecting group is removed by treatment of the compound 1.3 with 8M methanesulfonic acid in acetonitrile, as described in Tet. Asym., 13, 2000, 1201, to afford the amine 1.4. The latter compound is then reacted with a carboxylic acid 1.5, to afford the amide 1.6. The preparation of the carboxylic acid reactants 1.5 is described below, (Schemes 41, 42). The reaction is performed under similar conditions to those described above for the preparation of the amide 1.3. Preferably, equimolar amounts of the amine 1.4 and the carboxylic acid 1.6 are reacted in tetrahydrofuran solution at ambient temperature in the presence of dicyclohexylcarbodiimide and hydroxybenztriazole, for example as described in EP 574135, to yield the amide 1.6. The BOC protecting group is then removed from the product 1.6 to afford the amine 1.7, using similar conditions to those described above for the removal of BOC protecting group from the compound 1.3. Preferably, the BOC group is removed by treatment of the substrate 1.6 with a 4M solution of hydrogen chloride in dioxan at 0°, for example as described in EP 574135, to give the amine product 1.7. The amine is then reacted with a carboxylic acid 1.8, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide 1.9. The preparation of the carboxylic acids 1.8 is described below in Schemes 45 - 49. The reaction between the amine 1.7 and the carboxylic acid 1.8 is conducted under similar conditions to those described above for the preparation of the amides 1.3 and 1.6.

The procedures illustrated in Scheme 1 describe the preparation of the compounds 1.9 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 2 depicts the conversion of the compounds 1.9 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 1. Procedures for the conversion of the

substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

In the preceding and following schemes, the conversion of various substituents into the group link-P(O)(OR¹)₂ can be effected at any convenient stage of the synthetic sequence, as well as at the end. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures.

The phosphonate esters 5 - 12 in which the substituent R⁸CO is derived from one of the carboxylic acids C38 - C49, as shown in Chart 3c, incorporate a carbamate linkage. Various methods for the preparation of carbamate groups are described below in Scheme 102.

In the above and succeeding examples, the nature of the phosphonate ester group can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below (Scheme 103)

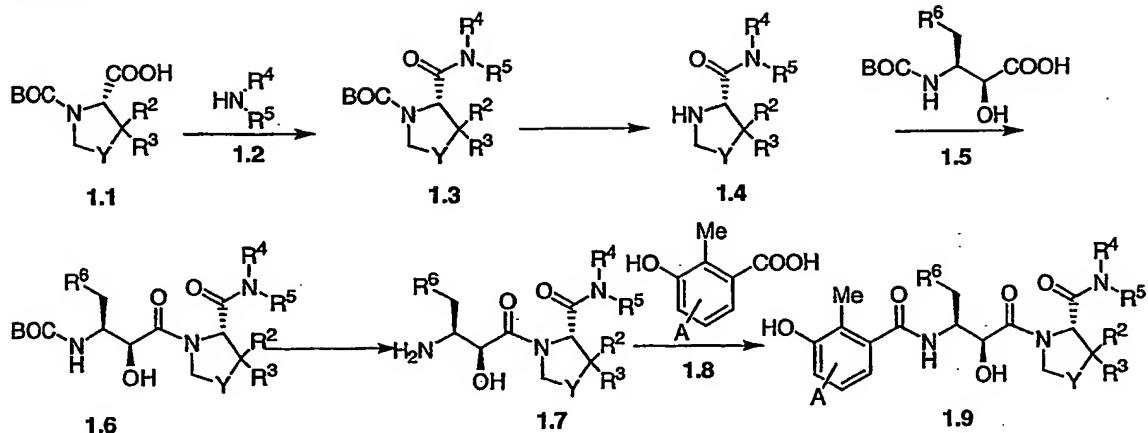
Preparation of the phosphonate ester intermediates 1 in which X is sulfur.

Schemes 3 and 4 illustrate the preparation of the phosphonate ester intermediates 1 in which X is sulfur. Scheme 3 illustrates the reaction of the amine 1.3, prepared as described in Scheme 1, with a carboxylic acid reagent 3.1, to give the amide product 3.2. The preparation of the carboxylic acid reagents 3.1 is described below in Schemes 43 and 44. The reaction between the carboxylic acid 3.1 and the amine 1.3 is performed under similar conditions to those described above for the preparation of the amide 1.6. The amide product 3.2 is then subjected to a deprotection reaction to remove the BOC substituent and afford the amine 3.3. The reaction is performed under similar conditions to those described in Scheme 1 for the removal of BOC protecting groups. The amine product 3.3 is then reacted with a carboxylic acid 1.8, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide product 3.4. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

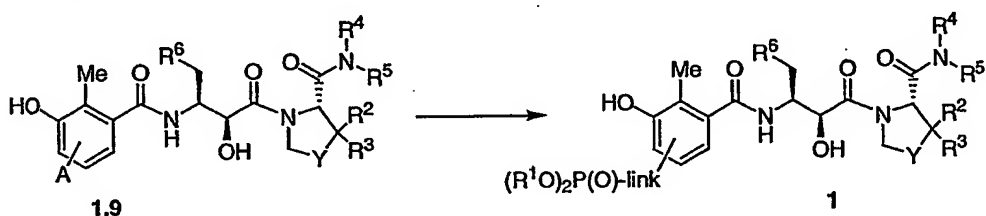
The procedures illustrated in Scheme 3 describe the preparation of the compounds 3.4 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], $[\text{NH}_2]$, Br, etc, as described herein.

- 5 Scheme 4 depicts the conversion of the compounds 3.4 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 1. Procedures for the conversion of the substituents [OH], [SH], $[\text{NH}_2]$, Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

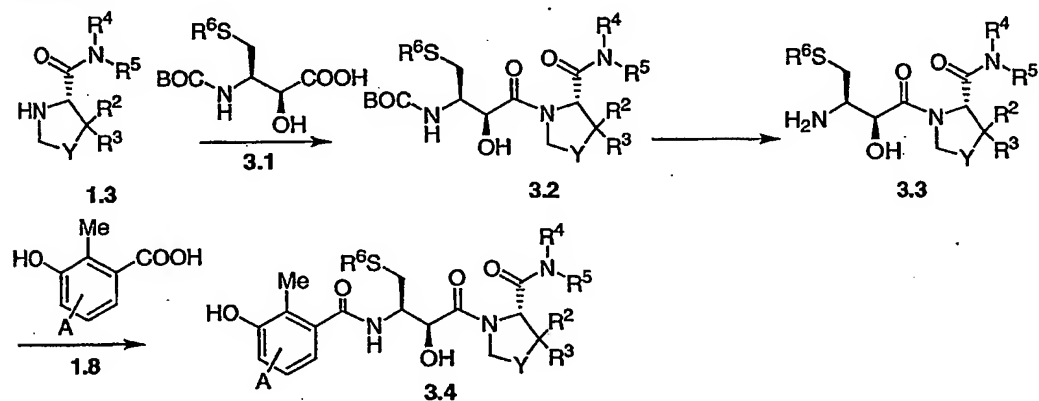
Scheme 1



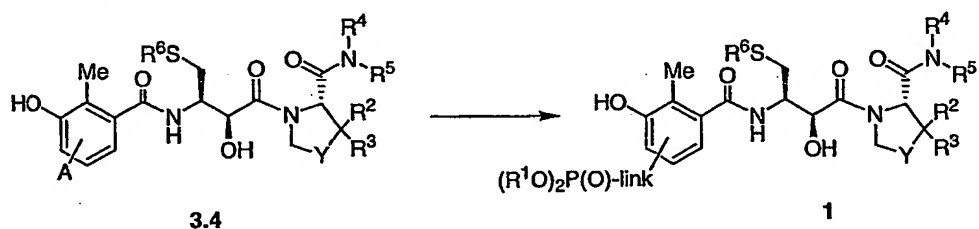
Scheme 2



Scheme 3



Scheme 4



Preparation of the phosphonate ester intermediates 2 in which X is a direct bond.

Schemes 5 and 6 depict the preparation of the intermediate phosphonate esters 2 in which X is direct bond. As shown in Scheme 5, the amine 1.7, prepared as described in Scheme 1, is reacted with a carboxylic acid 5.1, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide product 5.2. The preparation of the carboxylic acids 5.1 is described below in Schemes 50 - 56. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

The procedures illustrated in Scheme 5 describe the preparation of the compounds 5.2 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 6 depicts the conversion of the compounds 5.2 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 2 in which X is sulfur.

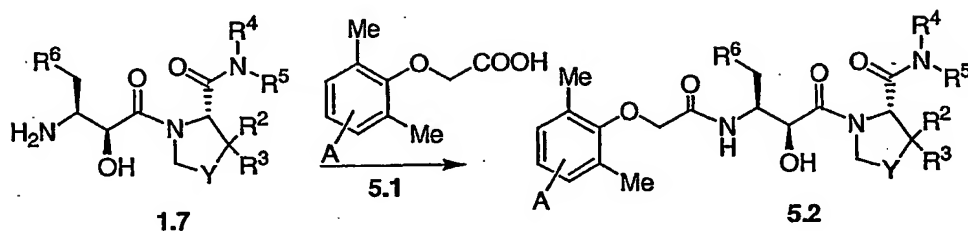
Schemes 7 and 8 depict the preparation of the intermediate phosphonate esters 2 in which X is sulfur. As shown in Scheme 7, the amine 3.3, prepared as described in Scheme 3, is reacted with a carboxylic acid 5.1, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide product 7.1. The preparation of the carboxylic acids 5.1 is described below in Schemes 50 - 56. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

The procedures illustrated in Scheme 7 describe the preparation of the compounds 7.1 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

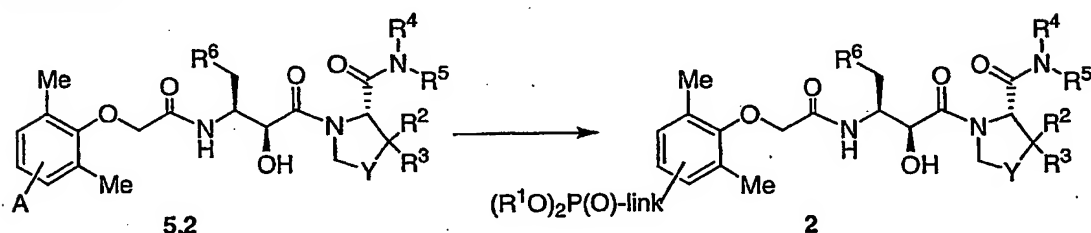
Scheme 8 depicts the conversion of the compounds 7.1 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 2. Procedures for the conversion of the

substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

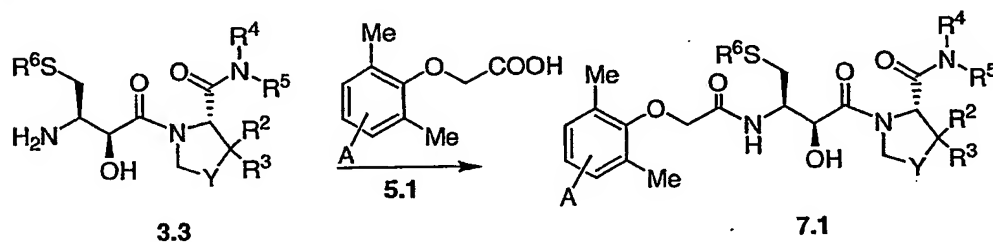
Scheme 5



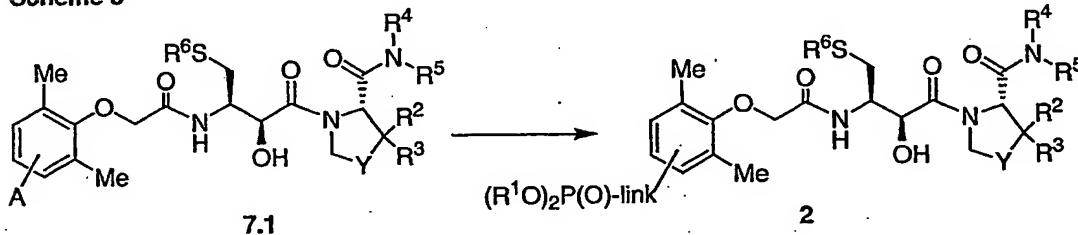
Scheme 6



Scheme 7



Scheme 8



5 Preparation of the phosphonate ester intermediates 3 in which X is a direct bond.

Schemes 9 and 10 depict the preparation of the intermediate phosphonate esters 3 in which X is direct bond. As shown in Scheme 9, the amine 1.7, prepared as described in Scheme 1, is reacted with a carboxylic acid 9.1, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br,

etc, as described herein, to afford the amide product 9.2. The preparation of the carboxylic acids 9.1 is described below in Schemes 57 - 60. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

- 5 The procedures illustrated in Scheme 9 describe the preparation of the compounds 9.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 10 depicts the conversion of the compounds 9.2 in which the group A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 3. Procedures for the conversion of the
10 substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 3 in which X is sulfur.

- 15 Schemes 11 and 12 depict the preparation of the intermediate phosphonate esters 3 in which X is sulfur. As shown in Scheme 11, the amine 3.3, prepared as described in Scheme 3, is reacted with a carboxylic acid 9.1, or an activated derivative thereof, in which the substituent A is the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide product 11.1. The preparation of the carboxylic acids 9.1
20 is described below in Schemes 57 - 60. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

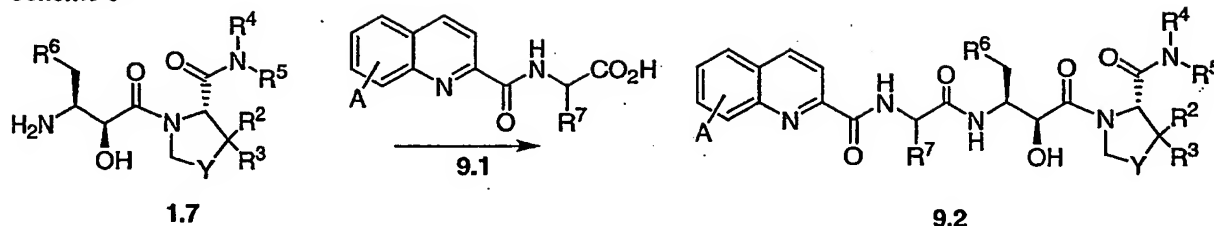
The procedures illustrated in Scheme 11 describe the preparation of the compounds 11.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

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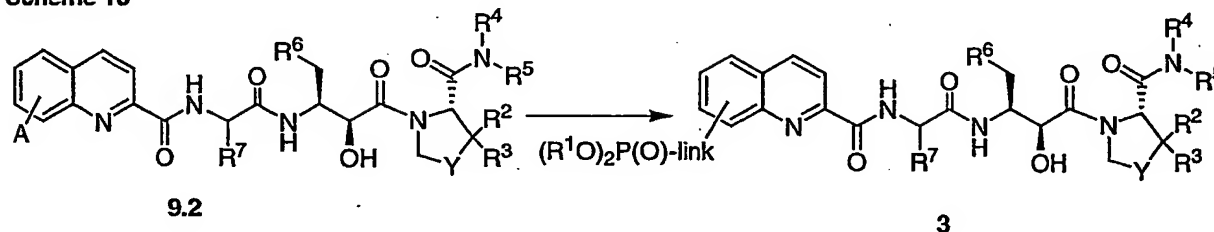
Scheme 12 depicts the conversion of the compounds 11.1 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 3. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

30

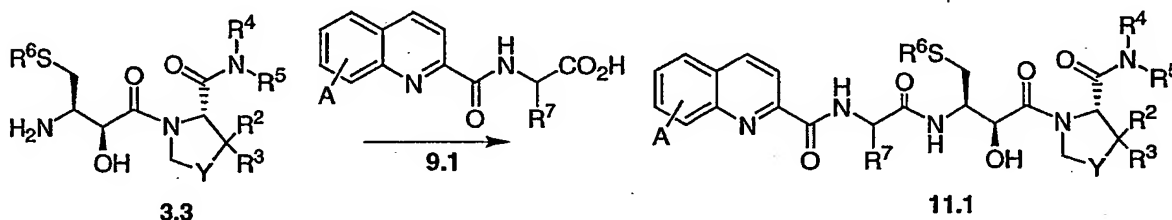
Scheme 9



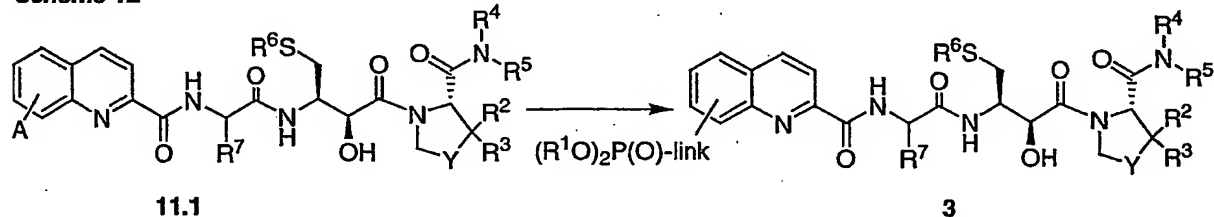
Scheme 10



Scheme 11



Scheme 12



Preparation of the phosphonate ester intermediates 4 in which X is a direct bond.

- 5 Schemes 13 and 14 depict the preparation of the intermediate phosphonate esters **4** in which X is direct bond. As shown in Scheme 13, the amine **1.7**, prepared as described in Scheme 1, is reacted with a carboxylic acid **13.1**, or an activated derivative thereof, in which the substituent A is the group link- $P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], NH_2 , Br, etc, as described herein, to afford the amide product **13.2**. The preparation of the carboxylic acids **13.1** is described below in Schemes 61 - 66. The amide forming reaction is performed
- 10 under similar conditions to those described above for the preparation of the amide **1.9**.

The procedures illustrated in Scheme 13 describe the preparation of the compounds 13.2 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

5 Scheme 14 depicts the conversion of the compounds 13.2 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 4. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 4 in which X is sulfur.

10

Schemes 15 and 16 depict the preparation of the intermediate phosphonate esters 4 in which X is sulfur. As shown in Scheme 15, the amine 3.3, prepared as described in Scheme 3, is reacted with a carboxylic acid 13.1, or an activated derivative thereof, in which the substituent A is the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], NH₂, Br, etc, as described herein, to afford the amide product 15.1. The preparation of the carboxylic acids 13.1 is described below in Schemes 61 - 66. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.9.

15

The procedures illustrated in Scheme 15 describe the preparation of the compounds 15.1 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

20

Scheme 16 depicts the conversion of the compounds 15.1 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 4. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

25

Preparation of the phosphonate ester intermediates 5 in which X is a direct bond.

Schemes 17 and 18 show the preparation of the intermediate phosphonate esters 5 in which X is a direct bond. As depicted in Scheme 17, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid 17.1, or an activated derivative thereof, to yield the amide product 17.2. The preparation of the carboxylic acids 17.1 in which the group A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, is

30

described in Schemes 67 – 71. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.6. The BOC protecting group is then removed from the product 17.2 to afford the amine 17.3. The deprotection reaction is performed using similar conditions to those described above in Scheme 1. The resultant amine 17.3 is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, 17.4 to give the amide 17.5. For those carboxylic acids R^8COOH listed in Charts 3a and 3b, the reaction is performed using similar conditions to those described above for the preparation of the amide 1.9, (Scheme 1); for those carboxylic acids R^8COOH listed in Chart 3c, the reaction is performed using conditions described below (Scheme 102) for the preparation of carbamates.

The procedures illustrated in Scheme 17 describe the preparation of the compounds 17.5 in which the substituent A is either the group $link-P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], $[NH_2]$, Br, etc, as described herein.

Scheme 18 depicts the conversion of the compounds 17.5 in which the A is a precursor to the substituent $link-P(O)(OR^1)_2$ into the compounds 5. Procedures for the conversion of the substituents [OH], [SH], $[NH_2]$, Br etc into the substituent $link-P(O)(OR^1)_2$ are described below in Schemes 45 - 101.

20 Preparation of the phosphonate ester intermediates 5 in which X is sulfur.

Schemes 19 and 20 show the preparation of the intermediate phosphonate esters 5 in which X is sulfur. As depicted in Scheme 19, the amine 1.4, prepared as described in Scheme 1, is reacted with the carboxylic acid 19.1, or an activated derivative thereof, to yield the amide product 19.2. The preparation of the carboxylic acids 19.1 in which the group A is either the group $link-P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], $[NH_2]$, Br, etc, is described in Schemes 72 - 83. The amide forming reaction is performed under similar conditions to those described above for the preparation of the amide 1.6. The BOC protecting group is then removed from the product 19.2 to afford the amine 19.3. The deprotection reaction is performed using similar conditions to those described above in Scheme 1. The resultant amine 19.3 is then reacted with a carboxylic acid R^8COOH or activated derivative thereof, 19.4 to give the amide 19.4. For those carboxylic acids R^8COOH listed in Charts 3a

and **3b**, the reaction is performed using similar conditions to those described above for the preparation of the amide **1.9**, (Scheme 1); for those carboxylic acids R^8COOH listed in Chart **3c**, the reaction is performed using conditions described below (Scheme 102) for the preparation of carbamates.

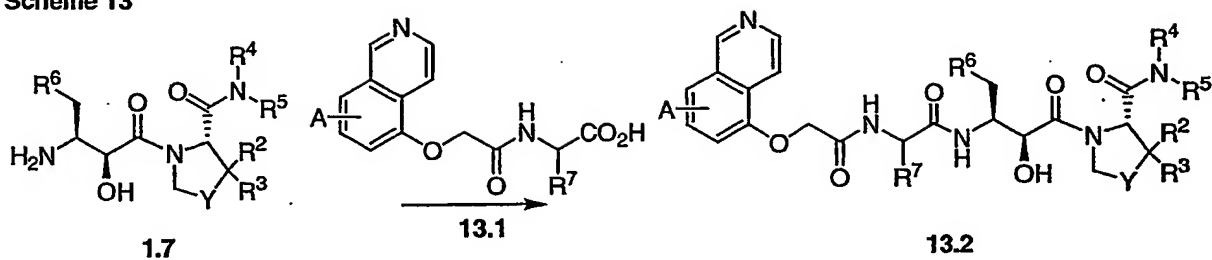
5

The procedures illustrated in Scheme 19 describe the preparation of the compounds **19.4** in which the substituent A is either the group $link-P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

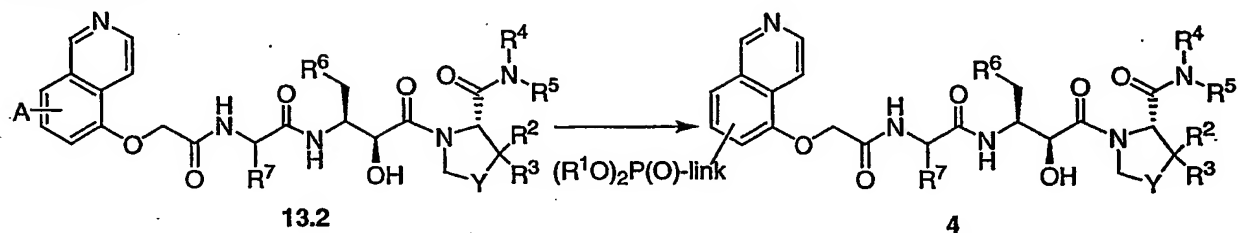
10

Scheme 20 depicts the conversion of the compounds **19.4** in which the A is a precursor to the substituent $link-P(O)(OR^1)_2$ into the compounds **5**. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $link-P(O)(OR^1)_2$ are described below in Schemes 45 - 101.

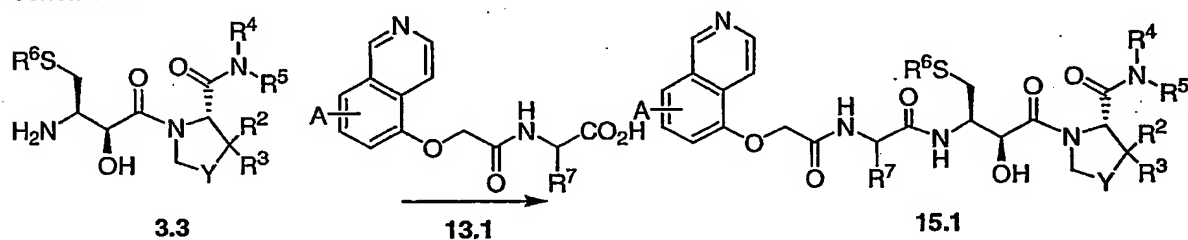
Scheme 13



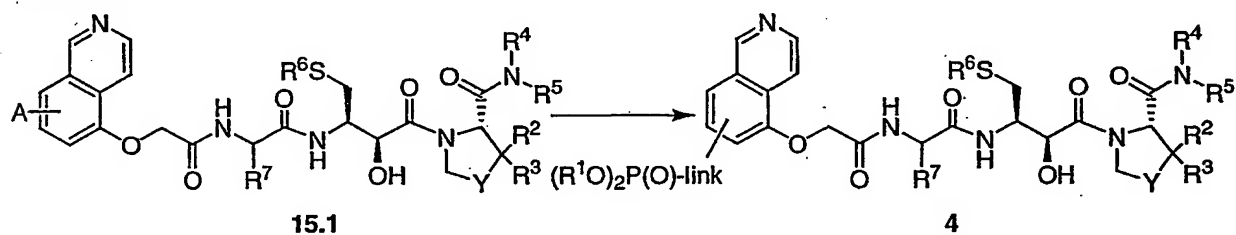
Scheme 14



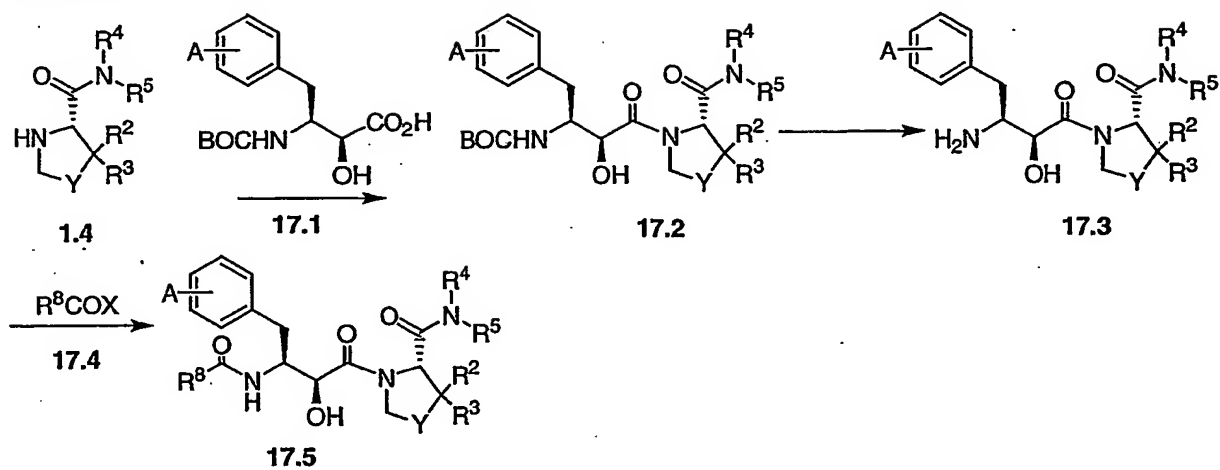
Scheme 15



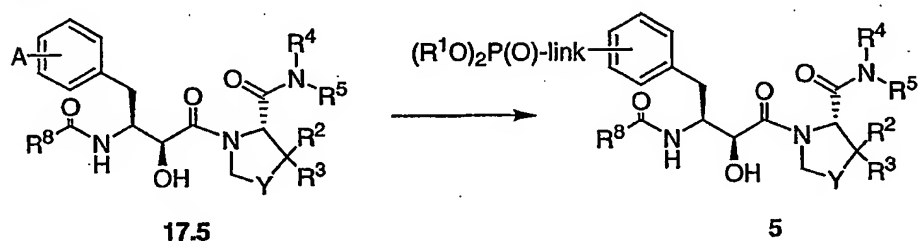
Scheme 16



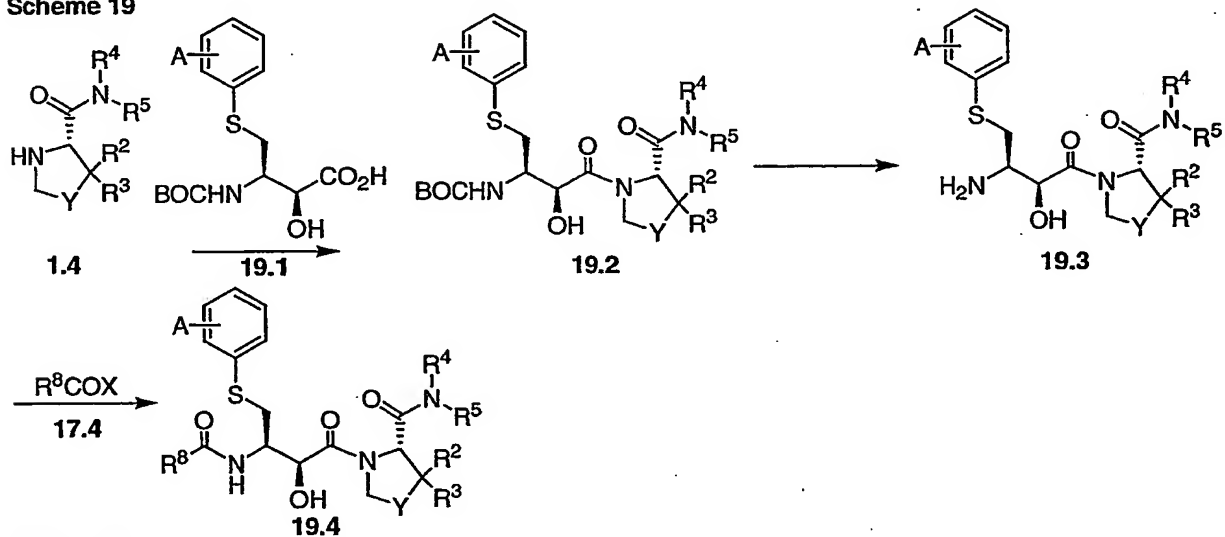
Scheme 17



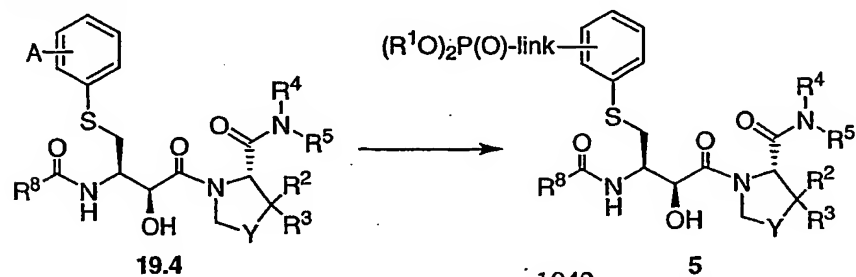
Scheme 18



Scheme 19



Scheme 20



Preparation of the phosphonate ester intermediates 6 in which X is a direct bond.

Schemes 21 and 22 illustrate the preparation of the phosphonate esters 6 in which X is a direct
5 bond. In this procedure, the carboxylic acid 21.1, in which the group A is the substituent link-
P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described
herein, is reacted with the amine 1.2 to afford the amide 21.2. The preparation of the
carboxylic acids 21.1 is described below in Schemes 98 - 101. The reaction is performed under
similar conditions to those described in Scheme 1 for the preparation of the amide 1.3. The
10 product 21.2 is then deprotected to yield the free amine 21.3, using the procedures described
above for the removal of BOC groups. The amine 21.3 is then converted, by reaction with the
carboxylic acid 1.5, into the amide 21.4, using the conditions described above for the
preparation of the amide 1.6. The amide 21.4 is then deprotected to afford the amine 21.5, and
the latter compound is acylated with the carboxylic acid 17.4 to give the amide 21.6.

15

The procedures illustrated in Scheme 21 describe the preparation of the compounds 21.6 in
which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto,
such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 22 depicts the conversion of the compounds 21.6 in which the A is a precursor to the
20 substituent link-P(O)(OR¹)₂ into the compounds 6. Procedures for the conversion of the
substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described
below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 6 in which X is sulfur.

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Schemes 23 and 24 illustrate the preparation of the phosphonate esters 6 in which X is sulfur.
In the procedure shown in Scheme 23, the amine 21.3, prepared as described in Scheme 21, is
reacted with the carboxylic acid 3.1 to afford the amide 23.1. The reaction is performed under
similar conditions to those described in Scheme 1 for the preparation of the amide 1.3. The
30 product 23.1 is then converted, by means of deprotection and acylation, as shown in Scheme
21 for the conversion of the compound 21.4 into the compound 21.6, into the amide product
23.2.

The procedures illustrated in Scheme 23 describe the preparation of the compounds 23.2 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

- 5 Scheme 24 depicts the conversion of the compounds 23.2 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1)_2$ into the compounds 6. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1)_2$ are described below in Schemes 45 - 101.

10 **Preparation of the phosphonate ester intermediates 7 in which X is a direct bond.**

- Schemes 25 and 26 illustrate the preparation of the phosphonate esters 7 in which X is a direct bond. As shown in Scheme 25, the carboxylic acid 1.1 is reacted with the amine 25.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein, to produce the amide 25.2. The reaction is performed using similar conditions to those described above for the preparation of the amide 1.3. The preparation of the amines 25.1 is described below, in Schemes 84 - 87. The amide product 25.2 is then transformed, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.2 into the compound 21.6, into the compound 25.3.

20

The procedures illustrated in Scheme 25 describe the preparation of the compounds 25.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

- 25 Scheme 25 depicts the conversion of the compounds 25.3 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1)_2$ into the compounds 7. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1)_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 7 in which X is sulfur.

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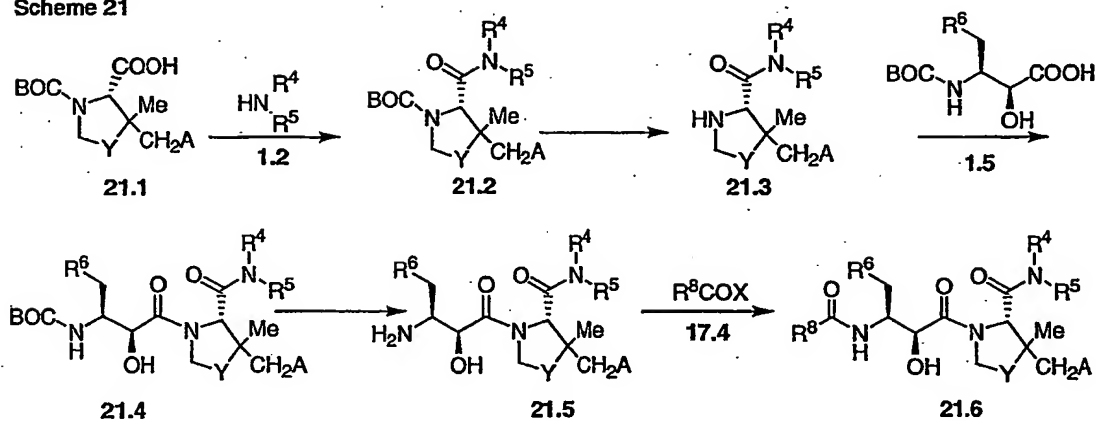
Schemes 27 and 28 illustrate the preparation of the phosphonate esters 7 in which X is sulfur. As shown in Scheme 27, the BOC-protected amine 25.2 is deprotected to yield the free amine

27.1, using the conditions previously described. The amine 27.1 is then reacted, as described above, with the carboxylic acid 3.1 to afford the amide 27.2. The latter compound is then transformed, as described above, (Scheme 23) into the product 27.3.

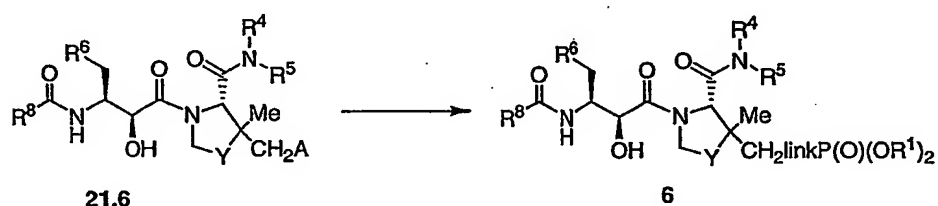
- 5 The procedures illustrated in Scheme 27 describe the preparation of the compounds 27.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 28 depicts the conversion of the compounds 27.3 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 7. Procedures for the conversion of the
10 substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

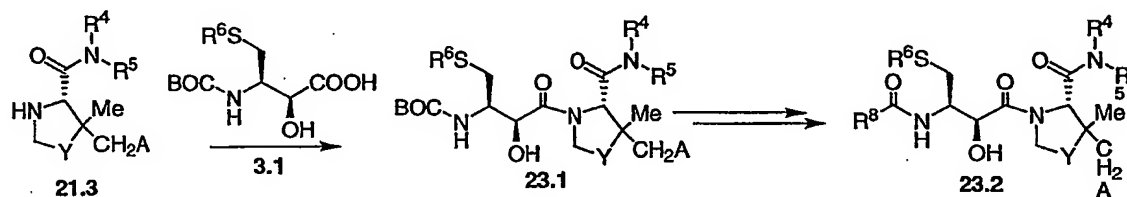
Scheme 21



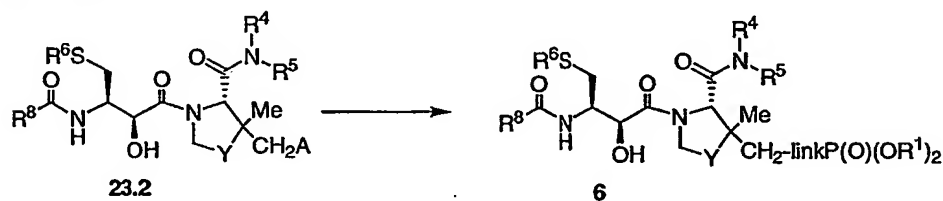
Scheme 22



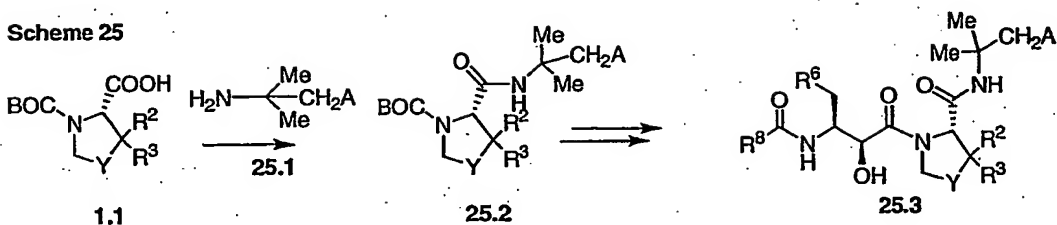
Scheme 23



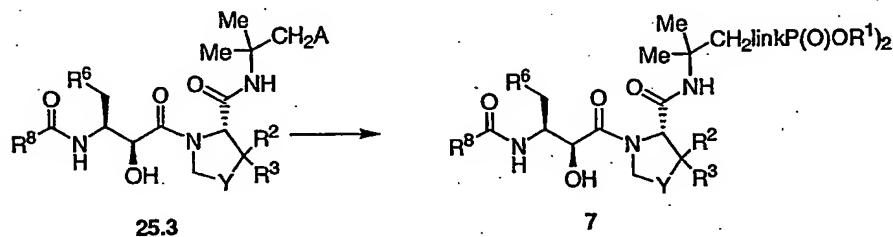
Scheme 24



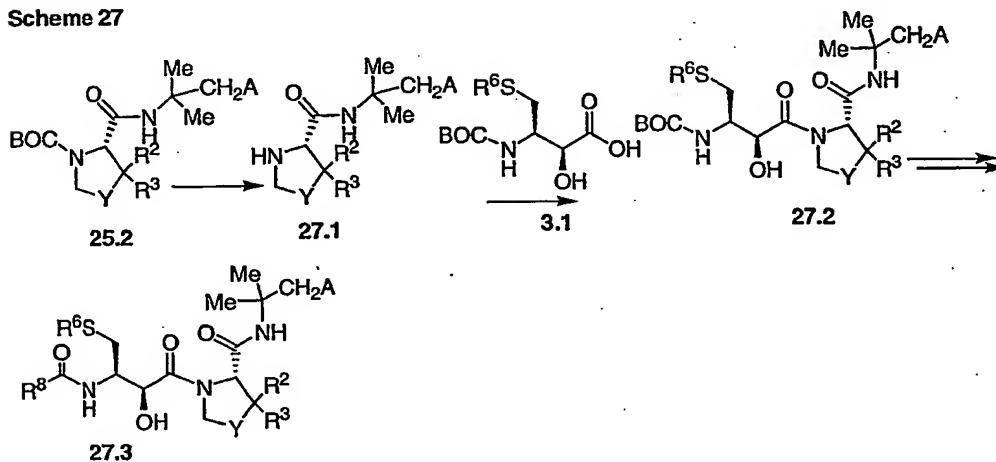
Scheme 25



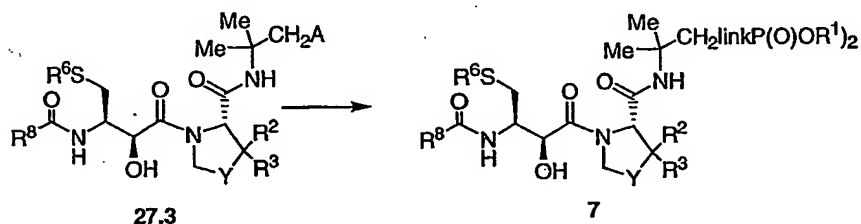
Scheme 26



Scheme 27



Scheme 28



Preparation of the phosphonate ester intermediates 8 in which X is a direct bond.

Schemes 29 and 30 illustrate the preparation of the phosphonate esters 8 in which X is a direct bond. As shown in Scheme 29, the carboxylic acid 1.1 is reacted with the amine 29.1, in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein, to produce the amide 29.2. The reaction is

performed using similar conditions to those described above for the preparation of the amide 1.3. The preparation of the amines 29.1 is described below, in Schemes 86 - 88. The amide product 29.2 is then transformed, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.2 into the compound 21.6, into the compound 29.3.

5

The procedures illustrated in Scheme 29 describe the preparation of the compounds 29.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 30 depicts the conversion of the compounds 29.3 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1)_2$ into the compounds 8. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1)_2$ are described below in Schemes 45 - 101.

10

Preparation of the phosphonate ester intermediates 8 in which X is sulfur.

15

Schemes 31 and 32 illustrate the preparation of the phosphonate esters 8 in which X is sulfur. As shown in Scheme 31, the BOC-protected amine 29.2 is deprotected to yield the free amine 31.1, using the conditions previously described. The amine 31.1 is then reacted, as described above, with the carboxylic acid 3.1 to afford the amide 31.2. The latter compound is then transformed, as described above, (Scheme 23) into the product 31.3.

20

The procedures illustrated in Scheme 31 describe the preparation of the compounds 31.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1)_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

25

Scheme 32 depicts the conversion of the compounds 31.3 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1)_2$ into the compounds 8. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1)_2$ are described below in Schemes 45 - 101.

30

Preparation of the phosphonate ester intermediates 9 in which X is a direct bond.

- Schemes 33 and 34 illustrate the preparation of the phosphonate esters 9 in which X is a direct bond. As shown in Scheme 33, the carboxylic acid 1.5 is reacted with the amine 33.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein, to produce the amide 33.2. The reaction is performed using similar conditions to those described above for the preparation of the amide 1.6 in Scheme 1. The preparation of the amines 33.1 is described below, in Schemes 91 - 97. The amide product 33.2 is then transformed into the compound 33.3, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.4 into the compound 21.6.
- The procedures illustrated in Scheme 33 describe the preparation of the compounds 33.3 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.
- Scheme 34 depicts the conversion of the compounds 33.3 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 9. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 9 in which X is sulfur.

- Schemes 35 and 36 illustrate the preparation of the phosphonate esters 9 in which X is sulfur. As shown in Scheme 35 the amine 33.2 is transformed into 35.1 by similar means described above (Scheme 23) for converting 21.3 into 23.2.
- The procedures illustrated in Scheme 35 describe the preparation of the compounds 35.1 in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.
- Scheme 36 depicts the conversion of the compounds 35.1 in which the A is a precursor to the substituent $\text{link-P(O)(OR}^1\text{)}_2$ into the compounds 9. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent $\text{link-P(O)(OR}^1\text{)}_2$ are described below in Schemes 45 - 101.

Preparation of the phosphonate ester intermediates 10 in which X is a direct bond.

Schemes 37 and 38 illustrate the preparation of the phosphonate esters 10 in which X is a direct bond. As shown in Scheme 37, the carboxylic acid 1.5 is reacted with the amine 37.1, in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein, to produce the amide 37.2. The reaction is performed using similar conditions to those described above for the preparation of the amide 1.6. The preparation of the amines 37.1 is described below, in Scheme 91-97. The amide product 37.2 is then transformed into the compound 37.3, using the sequence of reactions shown in Scheme 21 for the conversion of the amide 21.4 into the compound 21.6.

The procedures illustrated in Scheme 37 describe the preparation of the compounds 37.3 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 38 depicts the conversion of the compounds 37.3 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 10. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

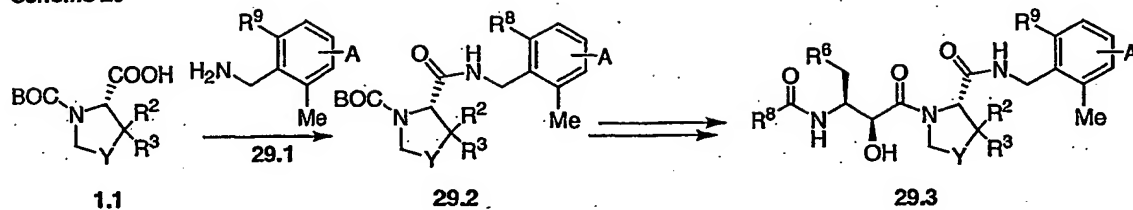
Preparation of the phosphonate ester intermediates 10 in which X is sulfur.

Schemes 39 and 40 illustrate the preparation of the phosphonate esters 10 in which X is sulfur. As shown in Scheme 39 the amine 37.1 is transformed into the product 39.1, as described above, (Scheme 23) for the conversion of 21.3 into 23.2.

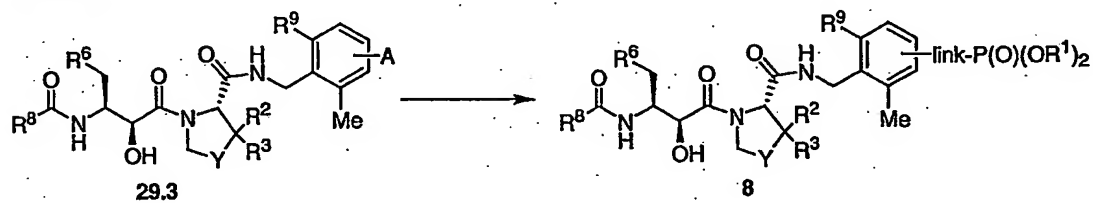
The procedures illustrated in Scheme 39 describe the preparation of the compounds 39.1 in which the substituent A is either the group link-P(O)(OR¹)₂, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein.

Scheme 40 depicts the conversion of the compounds 39.1 in which the A is a precursor to the substituent link-P(O)(OR¹)₂ into the compounds 10. Procedures for the conversion of the substituents [OH], [SH], [NH₂], Br etc into the substituent link-P(O)(OR¹)₂ are described below in Schemes 45 - 101.

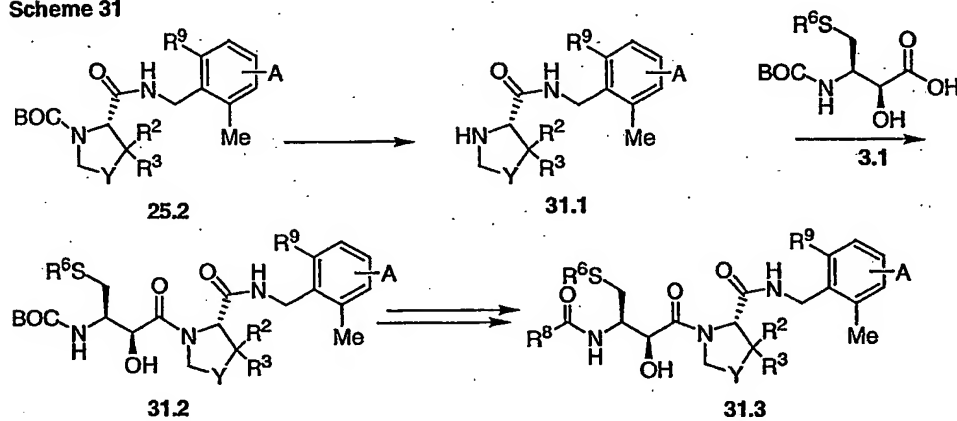
Scheme 29



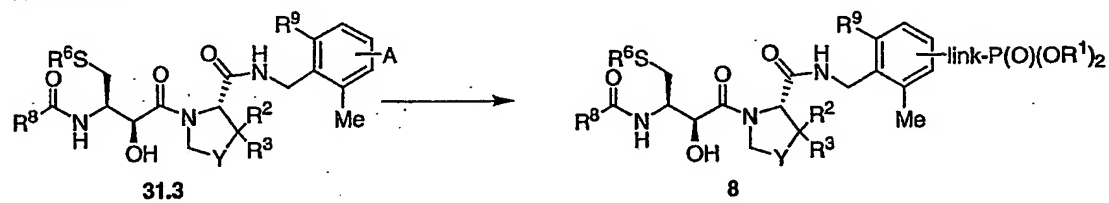
Scheme 30



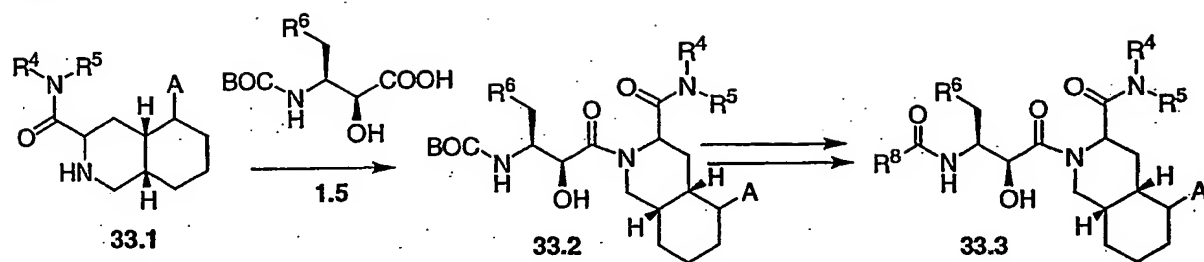
Scheme 31



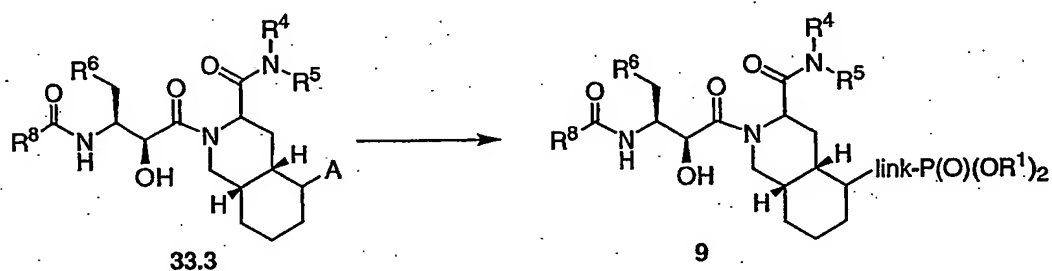
Scheme 32



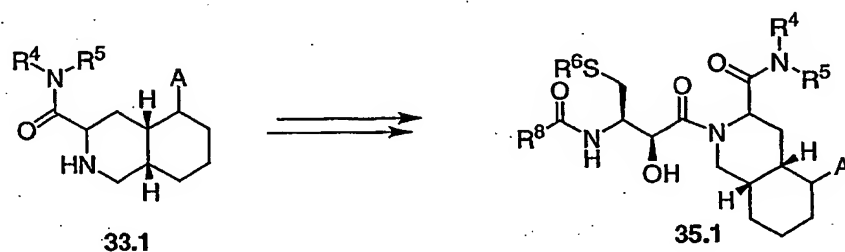
Scheme 33



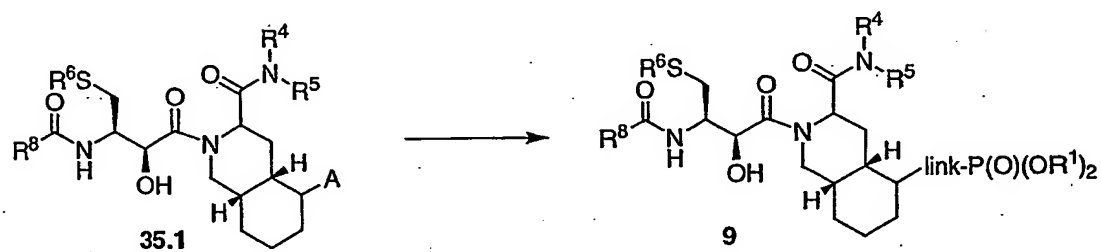
Scheme 34



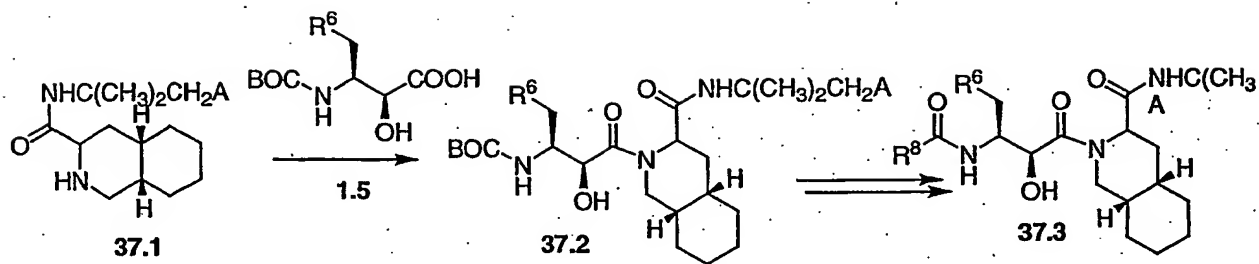
Scheme 35



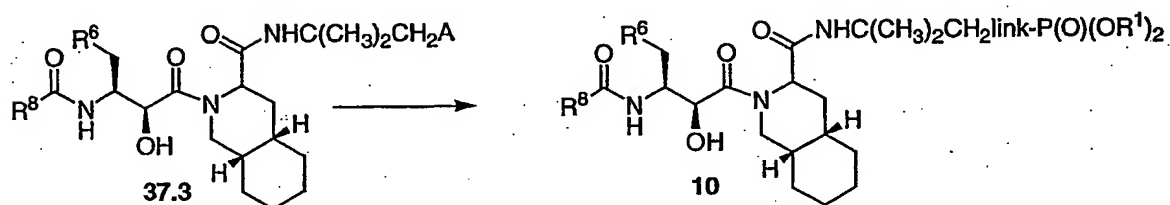
Scheme 36



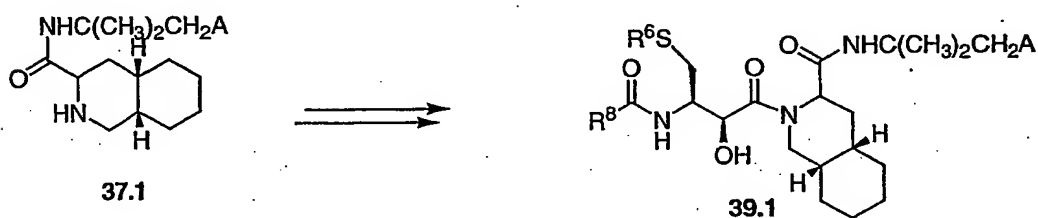
Scheme 37



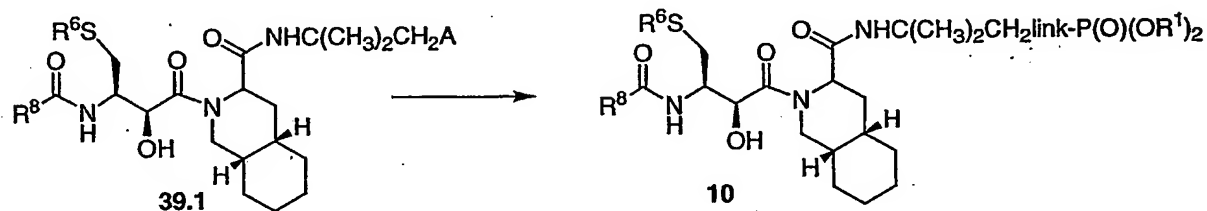
Scheme 38



Scheme 39



Scheme 40



Preparation of the BOC-protected aminohydroxy phenylbutanoic acids 1.5.

- 5 The preparation of the butanoic acid derivatives 1.5 in which R⁶ is phenyl is described, for example, in Tet. Asym., 2002, 13, 1201, Eur. J. Med. Chem., 2000, 35, 887, Chem. Pharm. Bull., 2000, 48, 1310, J. Med. Chem., 1994, 37, 2918, J. Chem. Res., 1999, 282 and J. Med.

Chem., 1993, 36, 211. The analogs 1.5 in which the substituent R⁶ is as described in Chart 5 are prepared by analogous reaction sequences.

Schemes 41 and 42 illustrate two alternative procedures for the preparation of the reactants 1.5. As shown in Scheme 41, the BOC-protected aminoacid 41.1 is converted into the corresponding aldehyde 41.3. Numerous methods are known for the conversion of carboxylic acids and derivatives into the corresponding aldehydes, for example as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 619-627. The conversion is effected by direct reduction of the carboxylic acid, for example employing diisobutyl aluminum hydride, as described in J. Gen. Chem. USSR., 34, 1021, 1964, or alkyl borane reagents, for example as described in J. Org. Chem., 37, 2942, 1972. Alternatively, the carboxylic acid is converted into an amide, such as the N-methoxy N-methyl amide, and the latter compound is reduced with lithium aluminum hydride, for example as described in J. Med. Chem., 1994, 37, 2918, to afford the aldehyde 41.3. Alternatively, the carboxylic acid is reduced to the corresponding carbinol 41.2. The reduction of carboxylic acids to carbinols is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 548ff. The reduction reaction is performed by the use of reducing agents such as borane, as described in J. Am. Chem. Soc., 92, 1637, 1970, or by lithium aluminum hydride, as described in Org. Reac., 6, 649, 1951. The resultant carbinol 41.2 is then converted into the aldehyde 41.3 by means of an oxidation reaction. The oxidation of a carbinol to the corresponding aldehyde is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 604ff. The conversion is effected by the use of oxidizing agents such as pyridinium chlorochromate, as described in J. Org. Chem., 50, 262, 1985, or silver carbonate, as described in Compt. Rend. Ser. C., 267, 900, 1968, or dimethyl sulfoxide/acetic anhydride, as described in J. Am. Chem. Soc., 87, 4214, 1965. Preferably, the carbinol 41.2 is converted into the aldehyde 41.3 by oxidation with pyridine-sulfur trioxide in dimethyl sulfoxide, as described in Eur. J. Med. Chem., 35, 2000, 887. The aldehyde 41.3 is then transformed into the cyanohydrin 1.4. The transformation of an aldehyde into the corresponding cyanohydrin is effected by reaction with an alkali metal cyanide such as potassium cyanide, in an aqueous organic solvent mixture. Preferably, a solution of the aldehyde in ethyl acetate is reacted with an aqueous solution of potassium cyanide, as described in Eur. J. Med. Chem., 35, 2000, 887, to yield the cyanohydrin 41.4. Optionally, a

methanolic solution of the aldehyde is first treated with an aqueous solution of sodium bisulfite, and the bisulfite adduct which is formed in situ is then reacted with an aqueous solution of sodium cyanide, as described in J. Med. Chem., 37, 1994, 2918, to give the cyanohydrin 41.4. The latter compound is then hydrolyzed to afford the hydroxyacid product 41.5. The hydrolysis is effected under acidic conditions; for example, the cyanohydrin 41.4 is heated in a mixture of concentrated hydrochloric acid and dioxan, as described in Eur. J. Med. Chem., 35, 2000, 887, optionally in the presence of anisole, as described in J. Med. Chem., 37, 1994, 2918, to afford the hydroxyacid product, from which the (2S), (3S) isomer 41.5 is isolated. The BOC protecting group is then attached, for example by reaction of the aminoacid 41.5 with BOC anhydride in aqueous tetrahydrofuran containing triethylamine, as described in Eur. J. Med. Chem., 35, 2000, 887.

Alternatively, the BOC-protected aminohydroxy phenylbutanoic acids 1.5 are obtained by means of the reaction sequence shown in Scheme 42. In this sequence, the N, N-dibenzyl aminoacid ester 42.1, prepared as described in Tet., 1995, 51, 6397, is converted, using the procedures described above in Scheme 41, into the corresponding aldehyde 42.2. The latter compound is then reacted with a silylmethyl Grignard reagent, for example isopropoxydimethylsilylmethylmagnesium chloride 42.3, to give the carbinol product 42.4. Preferably, the aldehyde and ca. two molar equivalents of the Grignard reagent are reacted in tetrahydrofuran solution at 0°, as described in Tet. Asym., 2002, 13, 1201. The silyl carbinol 42.4 is then reacted with aqueous ammonium chloride, as described in Tet. Asym., 2002, 13, 1201, to give the diol 42.5. The N-benzyl groups are then removed to afford the free amine 42.6. The removal of N-benzyl groups is described, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 365. Benzyl groups are removed by catalytic hydrogenation in the presence of hydrogen or a hydrogen donor, by reduction with sodium in ammonia, by treatment with trichloroethyl chloroformate, or by oxidation, for example by the use of ruthenium tetroxide or 3-chloroperoxybenzoic acid and ferrous chloride. Preferably, the debenzylation is effected by hydrogenation of the substrate 42.5 in ethanol at ca 50° in the presence of 5% palladium on carbon catalyst, as described in Tet. Asym., 2002, 13, 1201, to produce the amine 42.6. The BOC protecting group is then attached using the procedures described above, and the resultant product 42.7 is oxidized to give the carboxylic acid 1.5. The oxidation of carbinols to

afford the corresponding carboxylic acid is described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 835. The conversion can be effected by the use of oxidizing agents such as chromium trioxide in acetic acid, potassium permanganate, ruthenium tetroxide or silver oxide. Preferably, the transformation is effected by the use of sodium chlorite and sodium hypochlorite in aqueous acetonitrile in the presence of a pH 6.7 phosphate buffer and a catalytic amount of 2,2,6,6-tetramethylpiperidin-1-oxyl, as described in Tet. Asym., 2002, 13, 1201, to afford the carboxylic acid 1.5.

Preparation of the BOC-protected aminohydroxy arylthiobutanoic acids 3.1.

Schemes 43 and 44 illustrate two alternative methods for the preparation of the BOC-protected aminohydroxy arylthiobutanoic acids 3.1. As shown in Scheme 43, N, N-dibenzyl serine methyl ester 43.1, prepared as described in J. Org. Chem., 1986, 63, 1709, is converted into the methanesulfonate ester 43.2. The carbinol is reacted with methanesulfonyl chloride and triethylamine in toluene, as described in J. Org. Chem., 65, 2000, 1623, to produce the mesylate 43.2. The latter compound is then reacted with a thiophenol R⁶SH, in the presence of a base, to give the thioether 43.4. The displacement reaction is performed in an organic solvent such as dimethylformamide, or in an aqueous organic solvent mixture, in the presence of an organic base such as triethylamine or dimethylaminopyridine, or an inorganic base such as potassium carbonate and the like. Preferably, the reactants are combined in toluene solution in the presence of aqueous sodium hydroxide and a phase transfer catalyst such as tetrabutyl ammonium bromide, as described in J. Org. Chem., 65, 2000, 1623, to afford the product 43.4. The ester product is then transformed into the corresponding aldehyde 43.5, using the procedures described above (Scheme 41). The aldehyde is then converted, using the sequence of reactions shown in Scheme 41, into the BOC-protected aminohydroxy arylthiobutanoic acids 3.1.

Alternatively, as shown in Scheme 44, the aldehyde 43.5 is converted, using the sequence of reactions shown in Scheme 42, into the product 3.1. The component reactions of this sequence are performed under similar conditions to those described for the analogous reactions in Scheme 42.

Preparation of phosphonate-containing hydroxymethyl benzoic acids 1.8.

Schemes 45 - 49 illustrate methods for the preparation of phosphonate-containing hydroxymethyl benzoic acids 1.8 which are employed in the preparation of the phosphonate esters 1.

5 Scheme 45 illustrates a method for the preparation of hydroxymethylbenzoic acid reactants in which the phosphonate moiety is attached directly to the phenyl ring. In this method, a suitably protected bromo hydroxy methyl benzoic acid 45.1 is subjected to halogen-methyl exchange to afford the organometallic intermediate 45.2. This compound is reacted with a chlorodialkyl phosphite 45.3 to yield the phenylphosphonate ester 45.4, which upon deprotection affords the
10 carboxylic acid 45.5.

For example, 4-bromo-3-hydroxy-2-methylbenzoic acid, 45.6, prepared by bromination of 3-hydroxy-2-methylbenzoic acid, as described, for example, J. Am. Chem. Soc., 55, 1676, 1933, is converted into the acid chloride, for example by reaction with thionyl chloride. The acid chloride is then reacted with 3-methyl-3-hydroxymethyloxetane 45.7, as described in
15 Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 268, to afford the ester 45.8. This compound is treated with boron trifluoride at 0° to effect rearrangement to the orthoester 45.9, known as the OBO ester. This material is treated with a silylating reagent, for example tert-butyl chlorodimethylsilane, in the presence of a base such as imidazole, to yield the silyl ether 45.10. Halogen-metal exchange is performed by the
20 reaction of the substrate 45.10 with butyllithium, and the lithiated intermediate is then coupled with a chlorodialkyl phosphite 45.3, to produce the phosphonate 45.11. Deprotection, for example by treatment with 4-toluenesulfonic acid in aqueous pyridine, as described in Can. J. Chem., 61, 712, 1983, removes both the OBO ester and the silyl group, to produce the carboxylic acid 45.12.

25 Using the above procedures, but employing, in place of the bromo compound 45.6, different bromo compounds 45.1, there are obtained the corresponding products 45.5.

Scheme 46 illustrates the preparation of hydroxymethylbenzoic acid derivatives in which the phosphonate moiety is attached by means of a one-carbon link.

30 In this method, a suitably protected dimethyl hydroxybenzoic acid, 46.1, is reacted with a brominating agent, so as to effect benzylic bromination. The product 46.2 is reacted with a sodium dialkyl phosphite, 46.3, as described in J. Med. Chem., 1992, 35, 1371, to effect

displacement of the benzylic bromide to afford the phosphonate 46.4. Deprotection of the carboxyl function then yields the carboxylic acid 46.5.

For example, 2,5-dimethyl-3-hydroxybenzoic acid, 46.6, the preparation of which is described in Can. J. Chem., 1970, 48, 1346, is reacted with excess methoxymethyl chloride, as described
5 in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Second Edition 1990, p.17, to afford the ether ester 46.7. The reaction is performed in an inert solvent such as dichloromethane, in the presence of an organic base such as N-methylmorpholine or diisopropylethylamine. The product 46.7 is then reacted with a brominating agent, for example N-bromosuccinimide, in an inert solvent such as, for example, ethyl acetate, at reflux, to afford
10 the bromomethyl product 46.8. This compound is then reacted with a sodium dialkyl phosphite 46.3 in tetrahydrofuran, as described above, to afford the phosphonate 46.9. Deprotection, for example by brief treatment with a trace of mineral acid in methanol, as described in J. Chem. Soc. Chem. Comm., 1974, 298, then yields the carboxylic acid 46.10. Using the above procedures, but employing, in place of the methyl compound 46.6, different
15 methyl compounds 46.1, there are obtained the corresponding products 46.5.

Scheme 47 illustrates the preparation of phosphonate-containing hydroxymethylbenzoic acids in which the phosphonate group is attached by means of an oxygen or sulfur atom.

In this method, a suitably protected hydroxy- or mercapto-substituted hydroxy methyl benzoic
20 acid 47.1 is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate 47.2, to afford the coupled product 47.3, which upon deprotection affords the carboxylic acid 47.4.

For example, 3,6-dihydroxy-2-methylbenzoic acid, 47.5, the preparation of which is described in Yakugaku Zasshi 1971, 91, 257, is converted into the diphenylmethyl ester 47.6, by
25 treatment with diphenyldiazomethane, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 253. The product is then reacted with one equivalent of a silylating reagent, such as, for example, tert butylchlorodimethylsilane, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 77, to afford the mono-silyl ether 47.7. This compound is then reacted
30 with a dialkyl hydroxymethylphosphonate 47.2, under the conditions of the Mitsunobu reaction. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p.

448, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4 and in *Org. React.*, 1992, 42, 335. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, 1992, 42, 335-656. The reaction affords the coupled product **47.9**. Deprotection, for example by treatment with trifluoroacetic acid at ambient temperature, as described in *J. Chem. Soc., C*, 1191, 1966, then affords the phenolic carboxylic acid **47.9**.

Using the above procedures, but employing, in place of the phenol **47.5**, different phenols or thiophenols **47.1**, there are obtained the corresponding products **47.4**.

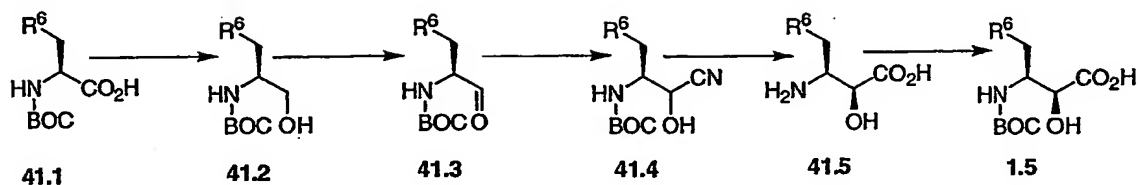
Scheme 48 depicts the preparation of phosphonate esters attached to the hydroxymethylbenzoic acid moiety by means of unsaturated or saturated carbon chains. In this method, a dialkyl alkenylphosphonate **48.2** is coupled, by means of a palladium catalyzed Heck reaction, with a suitably protected bromo substituted hydroxymethylbenzoic acid **48.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in *Acc. Chem. Res.*, 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. The product **48.3** is deprotected to afford the phosphonate **48.4**; the latter compound is subjected to catalytic hydrogenation to afford the saturated carboxylic acid **48.5**.

For example, 5-bromo-3-hydroxy-2-methylbenzoic acid **48.6**, prepared as described in WO 9218490, is converted as described above, into the silyl ether OBO ester **48.7**. This compound is coupled with, for example, a dialkyl 4-buten-1-ylphosphonate **48.8**, the preparation of which is described in *J. Med. Chem.*, 1996, 39, 949, using the conditions described above to afford the product **48.9**. Deprotection, or hydrogenation/deprotection, of this compound, as described above, then affords respectively the unsaturated and saturated products **48.10** and **48.11**.

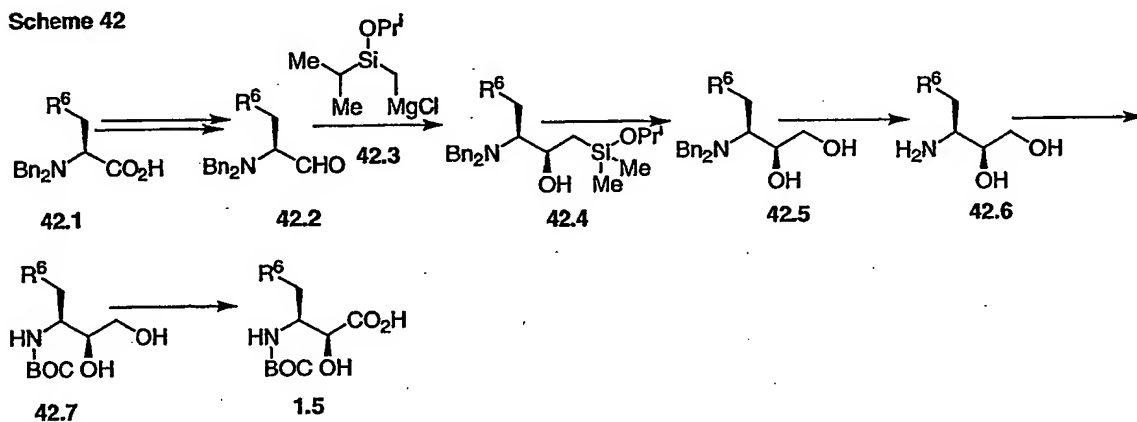
Using the above procedures, but employing, in place of the bromo compound 48.6, different bromo compounds 48.1, and/or different phosphonates 48.2, there are obtained the corresponding products 48.4 and 48.5.

- 5 Scheme 49 illustrates the preparation of phosphonate esters linked to the hydroxymethylbenzoic acid moiety by means of an aromatic ring.
- In this method, a suitably protected bromo-substituted hydroxymethylbenzoic acid 49.1 is converted to the corresponding boronic acid 49.2, by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82. The product is subjected to a
- 10 Suzuki coupling reaction with a dialkyl bromophenyl phosphonate 49.3. The product 49.4 is then deprotected to afford the diaryl phosphonate product 49.5.
- For example, the silylated OBO ester 49.6, prepared as described above, (Scheme 45), from 5-bromo-3-hydroxybenzoic acid, the preparation of which is described in J. Labelled. Comp. Radiopharm., 1992, 31, 175, is converted into the boronic acid 49.7, as described above. This
- 15 material is coupled with a dialkyl 4-bromophenyl phosphonate 49.8, prepared as described in J. Chem. Soc. Perkin Trans., 1977, 2, 789, using tetrakis(triphenylphosphine)palladium(0) as catalyst, in the presence of sodium bicarbonate, as described, for example, in Palladium reagents and catalysts J. Tsuji, Wiley 1995, p 218, to afford the diaryl phosphonate 49.9.
- Deprotection, as described above, then affords the benzoic acid 49.10.
- 20 Using the above procedures, but employing, in place of the bromo compound 49.6, different bromo compounds 49.1, and/or different phosphonates 49.3, there are obtained the corresponding carboxylic acid products 49.5.

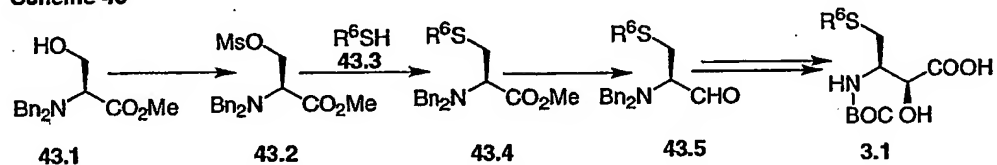
Scheme 41



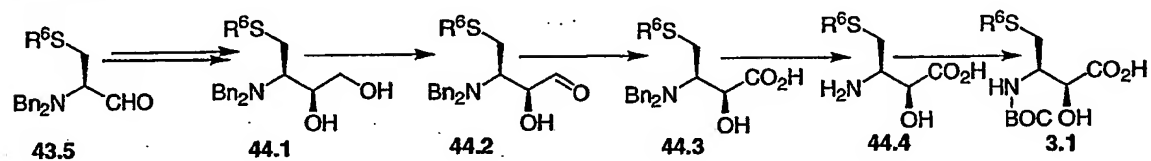
Scheme 42



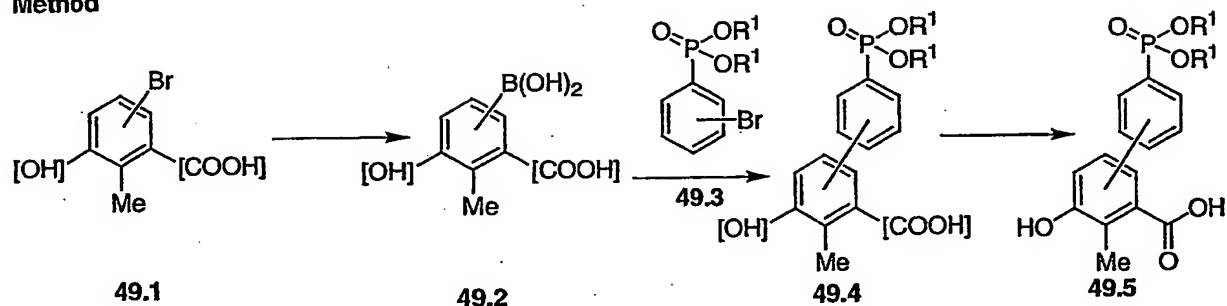
Scheme 43



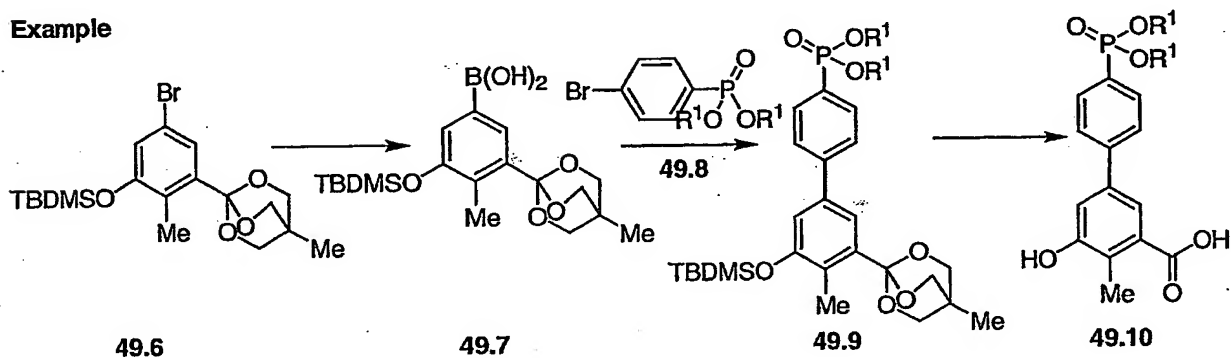
Scheme 44



Scheme 49
Method



Example



Preparation of dimethylphenoxyacetic acids 5.1 incorporating phosphonate moieties.

- 5 The preparation of the dimethylphenoxyacetic acids 5.1 incorporating phosphonate moieties which are used in the preparation of the phosphonate esters 2 is described in Schemes 50 - 56.

Scheme 50 illustrates two alternative methods by means of which 2,6-dimethylphenoxyacetic acids bearing phosphonate moieties may be prepared. The phosphonate group may be introduced into the 2,6-dimethylphenol moiety, followed by attachment of the acetic acid group, or the phosphonate group may be introduced into a preformed 2,6-dimethylphenoxyacetic acid intermediate. In the first sequence, a substituted 2,6-dimethylphenol 50.1, in which the substituent B is a precursor to the group link- $P(O)(OR^1)_2$, and in which the phenolic hydroxyl may or may not be protected, depending on the reactions to be performed, is converted into a phosphonate-containing compound 50.2. Methods for the conversion of the substituent B into the group link- $P(O)(OR^1)_2$ are described in Schemes 46 - 101.

The protected phenolic hydroxyl group present in the phosphonate-containing product 50.2 is then deprotected, using methods described below, to afford the phenol 50.3.

The phenolic product 50.3 is then transformed into the corresponding phenoxyacetic acid 50.4, in a two step procedure. In the first step, the phenol 50.3 is reacted with an ester of bromoacetic acid 50.4, in which R is an alkyl group or a protecting group. Methods for the protection of carboxylic acids are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff. The alkylation of phenols to afford phenolic ethers is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 446ff. Typically, the phenol and the alkylating agent are reacted together in the presence of an organic or inorganic base, such as, for example, diazabicyclononene, (DBN) or potassium carbonate, in a polar organic solvent such as, for example, dimethylformamide or acetonitrile.

Preferably, equimolar amounts of the phenol 50.3 and ethyl bromoacetate are reacted together in the presence of cesium carbonate, in dioxan at reflux temperature, for example as described in US Patent 5914332, to afford the ester 50.5.

The thus-obtained ester 50.5 is then hydrolyzed to afford the carboxylic acid 50.6. The methods used for this reaction depend on the nature of the group R. If R is an alkyl group such as methyl, hydrolysis can be effected by treatment of the ester with aqueous or aqueous alcoholic base, or by use of an esterase enzyme such as porcine liver esterase. If R is a protecting group, methods for hydrolysis are described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 224ff.

Preferably, the ester product 50.5 which R is ethyl is hydrolyzed to the carboxylic acid 50.6 by reaction with lithium hydroxide in aqueous methanol at ambient temperature, as described in US Patent 5914332.

Alternatively, an appropriately substituted 2,6-dimethylphenol 50.8, in which the substituent B is a precursor to the group $\text{link-P(O)(OR}^1\text{)}_2$, is transformed into the corresponding phenoxyacetic ester 50.7. The conditions employed for the alkylation reaction are similar to those described above for the conversion of the phenol 50.3 into the ester 50.5.

The phenolic ester 50.7 is then converted, by transformation of the group B into the group $\text{link-P(O)(OR}^1\text{)}_2$ followed by ester hydrolysis, into the carboxylic acid 50.6. The group B which is present in the ester 50.6 may be transformed into the group $\text{link-P(O)(OR}^1\text{)}_2$ either before or after hydrolysis of the ester moiety into the carboxylic acid group, depending on the nature of the chemical transformations required.

Schemes 51 - 56 illustrate the preparation of 2,6-dimethylphenoxyacetic acids incorporating phosphonate ester groups. The procedures shown can also be applied to the preparation of phenoxyacetic esters acids 50.7, with, if appropriate, modifications made according to the knowledge of one skilled in the art.

5

Scheme 51 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester which is attached to the phenolic group by means of a carbon chain incorporating a nitrogen atom. The compounds 51.4 are obtained by means of a reductive alkylation reaction between a 2,6-dimethylphenol aldehyde 51.1 and an aminoalkyl phosphonate ester 51.2. The preparation of amines by means of reductive amination procedures is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, p. 421. In this procedure, the amine component 51.2 and the aldehyde component 51.1 are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product 51.3. The amination product 51.3 is then converted into the phenoxyacetic acid compound 51.4, using the alkylation and ester hydrolysis procedures described above, (Scheme 50) For example, equimolar amounts of 4-hydroxy-3,5-dimethylbenzaldehyde 51.5 (Aldrich) and a dialkyl aminoethyl phosphonate 51.6, the preparation of which is described in J. Org. Chem., 2000, 65, 676, are reacted together in the presence of sodium cyanoborohydride and acetic acid, as described, for example, in J. Am. Chem. Soc., 91, 3996, 1969, to afford the amine product 51.7. The product is then converted into the acetic acid 51.8, as described above. Using the above procedures, but employing, in place of the aldehyde 51.5, different aldehydes 51.1, and/or different aminoalkyl phosphonates 51.2, the corresponding products 51.4 are obtained.

25

Scheme 52 depicts the preparation of 2,6-dimethylphenols incorporating a phosphonate group linked to the phenyl ring by means of a saturated or unsaturated alkylene chain. In this procedure, an optionally protected bromo-substituted 2,6-dimethylphenol 52.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenyl phosphonate 52.2. The coupling of aryl bromides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503. The aryl bromide and the olefin are coupled in a polar solvent such as

30

dimethylformamide or dioxan, in the presence of a palladium(0) or palladium (2) catalyst.

Following the coupling reaction, the product 52.3 is converted, using the procedures described above, (Scheme 50) into the corresponding phenoxyacetic acid 52.4. Alternatively, the olefinic product 52.3 is reduced to afford the saturated 2,6-dimethylphenol derivative 52.5. Methods

5 for the reduction of carbon-carbon double bonds are described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, or chemical reduction employing, for example, diborane or diimide. Following the reduction reaction, the product 52.5 is converted, as described above, (Scheme 50) into the corresponding phenoxyacetic acid 52.6.

10 For example, 3-bromo-2,6-dimethylphenol 52.7, prepared as described in Can. J. Chem., 1983, 61, 1045, is converted into the tert-butyldimethylsilyl ether 52.8, by reaction with chloro-tert-butyldimethylsilane, and a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition 1990 p. 77. The product 52.8 is reacted with an equimolar amount of a dialkyl allyl phosphonate
15 52.9, for example diethyl allylphosphonate (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride, in dimethylformamide at ca. 60°, to produce the coupled product 52.10. The silyl group is removed, for example by the treatment of the ether 52.10 with a solution of tetrabutylammonium fluoride in tetrahydrofuran, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the phenol 52.11. This compound is converted,
20 employing the procedures described above, (Scheme 50) into the corresponding phenoxyacetic acid 52.12. Alternatively, the unsaturated compound 52.11 is reduced, for example by catalytic hydrogenation employing 5% palladium on carbon as catalyst, in an alcoholic solvent such as methanol, as described, for example, in Hydrogenation Methods, by R. N. Rylander, Academic Press, 1985, Ch. 2, to afford the saturated analog 52.13. This compound is
25 converted, employing the procedures described above, (Scheme 50) into the corresponding phenoxyacetic acid 52.14.

Using the above procedures, but employing, in place of 3-bromo-2,6-dimethylphenol 52.7, different bromophenols 52.1, and/or different dialkyl alkenyl phosphonates 52.2, the corresponding products 52.4 and 52.6 are obtained.

30

Scheme 53 illustrates the preparation of phosphonate-containing 2,6-dimethylphenoxyacetic acids 53.1 in which the phosphonate group is attached to the 2,6-dimethylphenoxy moiety by

means of a carbocyclic ring. In this procedure, a bromo-substituted 2,6-dimethylphenol 53.2 is converted, using the procedures illustrated in Scheme 50, into the corresponding 2,6-dimethylphenoxyacetic ester 53.3. The latter compound is then reacted, by means of a palladium-catalyzed Heck reaction, with a cycloalkenone 53.4, in which n is 1 or 2. The coupling reaction is conducted under the same conditions as those described above for the preparation of the unsaturated phosphonate 52.3. (Scheme 52). The product 53.5 is then reduced catalytically, as described above for the reduction of the phosphonate 52.3, (Scheme 52), to afford the substituted cycloalkanone 53.6. The ketone is then subjected to a reductive amination procedure, by reaction with a dialkyl 2-aminoalkylphosphonate 53.7 and sodium triacetoxyborohydride, as described in J. Org. Chem., 61, 3849, 1996, to yield the amine phosphonate 53.8. The reductive amination reaction is conducted under the same conditions as those described above for the preparation of the amine 51.3 (Scheme 51). The resultant ester 53.8 is then hydrolyzed, as described above, to afford the phenoxyacetic acid 53.1.

For example, 4-bromo-2,6-dimethylphenol 53.9 (Aldrich) is converted, as described above, into the phenoxy ester 53.10. The latter compound is then coupled, in dimethylformamide solution at ca. 60°, with cyclohexenone 53.11, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, to yield the cyclohexenone 53.12. The enone is then reduced to the saturated ketone 53.13, by means of catalytic hydrogenation employing 5% palladium on carbon as catalyst. The saturated ketone is then reacted with an equimolar amount of a dialkyl aminoethylphosphonate 53.14, prepared as described in J. Org. Chem., 2000, 65, 676, in the presence of sodium cyanoborohydride, to yield the amine 53.15. Hydrolysis, employing lithium hydroxide in aqueous methanol at ambient temperature, then yields the acetic acid 53.16.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylphenol 53.9, different bromo-substituted 2,6-dimethylphenols 53.2, and/or different cycloalkenones 53.4, and/or different dialkyl aminoalkylphosphonates 53.7, the corresponding products 53.1 are obtained.

Scheme 54 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate group attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation reactions in which an optionally protected hydroxy, thio or amino-substituted 2,6-dimethylphenol 54.1 is reacted, in the

presence of a base such as, for example, potassium carbonate, and optionally in the presence of a catalytic amount of an iodide such as potassium iodide, with a dialkyl bromoalkyl phosphonate 54.2. The reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile at from ambient temperature to about 80°. The product of the alkylation reaction, 54.3 is then converted, as described above (Scheme 50) into the phenoxyacetic acid 54.4.

For example, 2,6-dimethyl-4-mercaptophenol 54.5, prepared as described in EP 482342, is reacted in dimethylformamide at ca. 60° with an equimolar amount of a dialkyl bromobutyl phosphonate 54.6, the preparation of which is described in Synthesis, 1994, 9, 909, in the presence of ca. 5 molar equivalents of potassium carbonate, to afford the thioether product 54.7. This compound is converted, employing the procedures described above, (Scheme 50) into the corresponding phenoxyacetic acid 54.8.

Using the above procedures, but employing, in place of 2,6-dimethyl-4-mercaptophenol 54.5, different hydroxy, thio or aminophenols 54.1, and/or different dialkyl bromoalkyl phosphonates 54.2, the corresponding products 54.4 are obtained.

Scheme 55 illustrates the preparation of 2,6-dimethylphenoxyacetic acids incorporating a phosphonate ester group attached by means of an aromatic or heteroaromatic group. In this procedure, an optionally protected hydroxy, mercapto or amino-substituted 2,6-dimethylphenol 55.1 is reacted, under basic conditions, with a bis(halomethyl)aryl or heteroaryl compound 55.2. Equimolar amounts of the phenol and the halomethyl compound are reacted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as potassium or cesium carbonate, or dimethylaminopyridine, to afford the ether, thioether or amino product 55.3. The product 55.3 is then converted, using the procedures described above, (Scheme 50) into the phenoxyacetic ester 55.4. The latter compound is then subjected to an Arbuzov reaction by reaction with a trialkylphosphite 55.5 at ca. 100° to afford the phosphonate ester 55.6. The preparation of phosphonates by means of the Arbuzov reaction is described, for example, in Handb. Organophosphorus Chem., 1992, 115. The resultant product 55.6 is then converted into the acetic acid 55.7 by hydrolysis of the ester moiety, using the procedures described above, (Scheme 50).

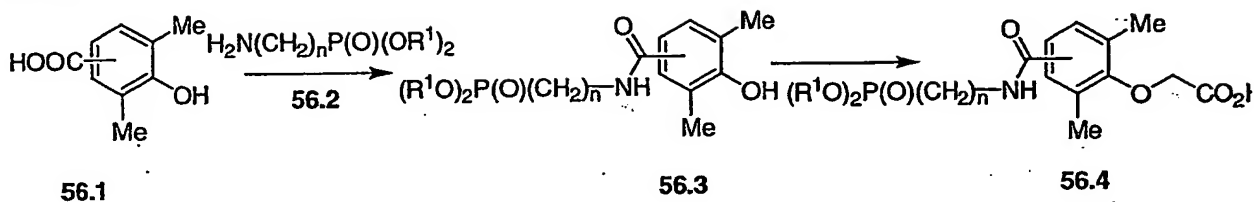
For example, 4-hydroxy-2,6-dimethylphenol 55.8 (Aldrich) is reacted with one molar equivalent of 3,5-bis(chloromethyl)pyridine, the preparation of which is described in Eur. J.

Inorg. Chem., 1998, 2, 163, to afford the ether 55.10. The reaction is conducted in acetonitrile at ambient temperature in the presence of five molar equivalents of potassium carbonate. The product 55.10 is then reacted with ethyl bromoacetate, using the procedures described above, (Scheme 50) to afford the phenoxyacetic ester 55.11. This product is heated at 100° for 3
5 hours with three molar equivalents of triethyl phosphite 55.12, to afford the phosphonate ester 55.13. Hydrolysis of the acetic ester moiety, as described above, for example by reaction with lithium hydroxide in aqueous ethanol, then affords the phenoxyacetic acid 55.14.
Using the above procedures, but employing, in place of the bis(chloromethyl) pyridine 55.9, different bis(halomethyl) aromatic or heteroaromatic compounds 55.2, and/or different
10 hydroxy, mercapto or amino-substituted 2,6-dimethylphenols 55.1 and/or different trialkyl phosphites 55.5, the corresponding products 55.7 are obtained.

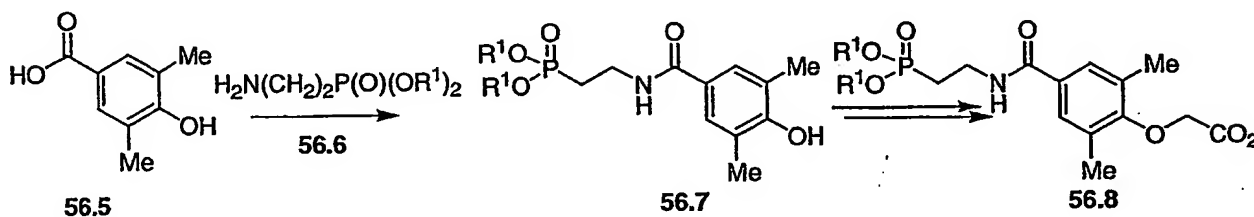
Scheme 56 illustrates the preparation of dimethylphenoxyacetic acids incorporating a phosphonate group attached by means of an amide group. In this procedure, a carboxy-
15 substituted 2,6-dimethylphenol 56.1 is reacted with a dialkyl aminoalkyl phosphonate 56.2 to afford the amide product 56.3. The amide-forming reaction is performed under similar conditions to those described above for the preparation of the amides 1.3 and 1.6. The product 56.3 is then transformed, as described above (Scheme 50) into the phenoxyacetic acid 56.4.
For example, 3,5-dimethyl-4-hydroxybenzoic acid 56.5 (Aldrich) is reacted with a dialkyl
20 aminoethylphosphonate 56.6, the preparation of which is described in J. Org. Chem., 2000, 65, 676, in tetrahydrofuran solution in the presence of dicyclohexylcarbodiimide to produce the amide 56.7. The product is then transformed, as described above, (Scheme 50) into the corresponding phenoxyacetic acid 56.8.
Using the above procedures, but employing, in place of 3,5-dimethyl-4-hydroxybenzoic acid
25 56.5, different carboxy-substituted 2,6-dimethylphenols 56.1, and/or different dialkyl aminoalkyl phosphonates 56.2, the corresponding products 56.4 are obtained.

Scheme 56

Method



Example



Preparation of quinoline 2-carboxylic acids 9.1 incorporating phosphonate moieties.

- 5 The reaction sequences depicted in Schemes 9 - 12 for the preparation of the phosphonate esters 3 employ a quinoline-2-carboxylic acid reactant 9.1 in which the substituent A is either the group link-P(O)(OR¹)₂ or a precursor thereto, such as [OH], [SH] Br etc.
- A number of suitably substituted quinoline-2-carboxylic acids are available commercially or are described in the chemical literature. For example, the preparations of 6-hydroxy, 6-amino and 6-bromoquinoline-2-carboxylic acids are described respectively in DE 3004370, J. Het.
- 10 Chem., 1989, 26, 929 and J. Labelled Comp. Radiopharm., 1998, 41, 1103, and the preparation of 7-aminoquinoline-2-carboxylic acid is described in J. Am. Chem. Soc., 1987, 109, 620. Suitably substituted quinoline-2-carboxylic acids can also be prepared by procedures known to those skilled in the art. The synthesis of variously substituted quinolines is described,
- 15 for example, in Chemistry of Heterocyclic Compounds, Vol. 32, G. Jones, ed., Wiley, 1977, p 93ff. Quinoline-2-carboxylic acids can be prepared by means of the Friedlander reaction, which is described in Chemistry of Heterocyclic Compounds, Vol. 4, R. C. Elderfield, ed., Wiley, 1952, p. 204.
- 20 Scheme 57 illustrates the preparation of quinoline-2-carboxylic acids by means of the Friedlander reaction, and further transformations of the products obtained. In this reaction sequence, a substituted 2-aminobenzaldehyde 57.1 is reacted with an alkyl pyruvate ester 57.2,

in the presence of an organic or inorganic base, to afford the substituted quinoline-2-carboxylic ester **57.3**. Hydrolysis of the ester, for example by the use of aqueous base, then afford the corresponding carboxylic acid **57.4**. The carboxylic acid product **57.4** in which X is NH₂ can be further transformed into the corresponding compounds **57.6** in which Z is OH, SH or Br. The latter transformations are effected by means of a diazotization reaction. The conversion of aromatic amines into the corresponding phenols and bromides by means of a diazotization reaction is described respectively in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, pages 167 and 94; the conversion of amines into the corresponding thiols is described in Sulfur Lett., 2000, 24, 123. The amine is first converted into the diazonium salt by reaction with nitrous acid. The diazonium salt, preferably the diazonium tetrafluoroborate, is then heated in aqueous solution, for example as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 83, to afford the corresponding phenol **57.6**, Y = OH. Alternatively, the diazonium salt is reacted in aqueous solution with cuprous bromide and lithium bromide, as described in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 138, to yield the corresponding bromo compound, **57.6**, Y = Br. Alternatively, the diazonium tetrafluoroborate is reacted in acetonitrile solution with a sulfhydryl ion exchange resin, as described in Sulfur Lett., 2000, 24, 123, to afford the thiol **57.6**, Y = SH. Optionally, the diazotization reactions described above can be performed on the carboxylic esters **57.3** instead of the carboxylic acids **57.5**.

For example, 2,4-diaminobenzaldehyde **57.7** (Apin Chemicals) is reacted with one molar equivalent of methyl pyruvate **57.2** in methanol, in the presence of a base such as piperidine, to afford methyl-7-aminoquinoline-2-carboxylate **57.8**. Basic hydrolysis of the product, employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid **57.9**. The amino-substituted carboxylic acid is then converted into the diazonium tetrafluoroborate **57.10** by reaction with sodium nitrite and tetrafluoroboric acid. The diazonium salt is heated in aqueous solution to afford the 7-hydroxyquinoline-2-carboxylic acid, **57.11**, Z = OH. Alternatively, the diazonium tetrafluoroborate is heated in aqueous organic solution with one molar equivalent of cuprous bromide and lithium bromide, to afford 7-bromoquinoline-2-carboxylic acid **57.11**, Z = Br. Alternatively, the diazonium tetrafluoroborate **57.10** is reacted in acetonitrile solution with the sulfhydryl form of an ion exchange resin, as

described in Sulfur Lett., 2000, 24, 123, to prepare 7-mercaptoquinoline-2-carboxylic acid 57.11, Z = SH.

Using the above procedures, but employing, in place of 2,4-diaminobenzaldehyde 57.7, different aminobenzaldehydes 57.1, the corresponding amino, hydroxy, bromo or mercapto-substituted quinoline-2-carboxylic acids 57.6 are obtained. The variously substituted quinoline carboxylic acids and esters can then be transformed, as described herein, (Schemes 58 – 60) into phosphonate-containing derivatives.

Scheme 58 depicts the preparation of quinoline-2-carboxylic acids incorporating a phosphonate moiety attached to the quinoline ring by means of an oxygen or a sulfur atom. In this procedure, an amino-substituted quinoline-2-carboxylate ester 58.1 is transformed, via a diazotization procedure as described above (Scheme 57) into the corresponding phenol or thiol 58.2. The latter compound is then reacted with a dialkyl hydroxymethylphosphonate 58.3, under the conditions of the Mitsunobu reaction, to afford the phosphonate ester 58.4. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p. 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products 58.4. Basic hydrolysis of the ester group, for example employing one molar equivalent of lithium hydroxide in aqueous methanol, then yields the carboxylic acid 58.5. The product is then coupled with a suitably protected aminoacid derivative 58.6 to afford the amide 58.7. The reaction is performed under similar conditions to those described above for the preparation of the amide 1.6 (Scheme 1). The ester protecting group is then removed to yield the carboxylic acid 58.8.

For example, methyl 6-amino-2-quinoline carboxylate 58.9, prepared as described in J. Het. Chem., 1989, 26, 929, is converted, by means of the diazotization procedure described above, into methyl 6-mercaptoquinoline-2-carboxylate 58.10. This material is reacted with a dialkyl hydroxymethylphosphonate 58.11 (Aldrich) in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solution, to afford the thioether 58.12. Basic hydrolysis

then afford the carboxylic acid 58.13. The latter compound is then converted, as described above, into the aminoacid derivative 58.16.

Using the above procedures, but employing, in place of methyl 6-amino-2-quinoline carboxylate 58.9, different aminoquinoline carboxylic esters 58.1, and/or different dialkyl hydroxymethylphosphonates 58.3 the corresponding phosphonate ester products 58.8 are obtained.

Scheme 59 illustrates the preparation of quinoline-2-carboxylic acids incorporating phosphonate esters attached to the quinoline ring by means of a saturated or unsaturated carbon chain. In this reaction sequence, a bromo-substituted quinoline carboxylic ester 59.1 is coupled, by means of a palladium-catalyzed Heck reaction, with a dialkyl alkenylphosphonate 59.2. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Thus, Heck coupling of the bromo compound 59.1 and the olefin 59.2 affords the olefinic ester 59.3. Hydrolysis, for example by reaction with lithium hydroxide in aqueous methanol, or by treatment with porcine liver esterase, then yields the carboxylic acid 59.4. The latter compound is then transformed, as described above, into the homolog 59.5. Optionally, the unsaturated carboxylic acid 59.4 can be reduced to afford the saturated analog 59.6. The reduction reaction can be effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically. The product 59.6 is then converted, as described above (Scheme 58) into the aminoacid derivative 59.7.

For example, methyl 7-bromoquinoline-2-carboxylate, 59.8, prepared as described in J. Labelled Comp. Radiopharm., 1998, 41, 1103, is reacted in dimethylformamide at 60° with a dialkyl vinylphosphonate 59.9 (Aldrich) in the presence of 2 mol% of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 59.10. The product is then reacted with lithium hydroxide in aqueous tetrahydrofuran to produce the carboxylic acid 59.11. The latter compound is reacted with diimide, prepared by basic

hydrolysis of diethyl azodicarboxylate, as described in *Angew. Chem. Int. Ed.*, 4, 271, 1965, to yield the saturated product **59.12**. The latter compound is then converted, as described above, into the aminoacid derivative **59.13**. The unsaturated product **59.11** is similarly converted into the analog **59.14**.

- 5 Using the above procedures, but employing, in place of methyl 6-bromo-2-quinolinecarboxylate **59.8**, different bromoquinoline carboxylic esters **59.1**, and/or different dialkyl alkenylphosphonates **59.2**, the corresponding phosphonate ester products **59.5** and **59.7** are obtained.
- 10 Scheme **60** depicts the preparation of quinoline-2-carboxylic acid derivatives **60.5** in which the phosphonate group is attached by means of a nitrogen atom and an alkylene chain. In this reaction sequence, a methyl aminoquinoline-2-carboxylate **60.1** is reacted with a phosphonate aldehyde **60.2** under reductive amination conditions, to afford the aminoalkyl product **60.3**. The preparation of amines by means of reductive amination procedures is described, for
- 15 example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, p 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in
- 20 the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The ester product **60.3** is then hydrolyzed to yield the free carboxylic acid **60.4**. The latter compound is then converted, as described above, into the aminoacid derivative **60.5**.
- For example, methyl 7-aminoquinoline-2-carboxylate **60.6**, prepared as described in *J. Am.*
- 25 *Chem. Soc.*, 1987, 109, 620, is reacted with a dialkyl formylmethylphosphonate **60.7** (Aurora) in methanol solution in the presence of sodium borohydride, to afford the alkylated product **60.8**. The ester is then hydrolyzed, as described above, to yield the carboxylic acid **60.9**. The latter compound is then converted, as described above, into the aminoacid derivative **60.10**. Using the above procedures, but employing, in place of the formylmethyl phosphonate **60.7**,
- 30 different formylalkyl phosphonates **60.2**, and/or different aminoquinolines **60.1**, the corresponding products **60.5** are obtained.

Preparation of 5-hydroxyisoquinoline derivatives 13.1 incorporating phosphonate moieties.

Schemes 61 - 65 illustrate methods for the preparation of the 5-hydroxyisoquinoline derivatives 13.1 which are employed in the preparation of the intermediate phosphonate esters 4.

A number of substituted 5-hydroxyisoquinolines are commercially available, or have syntheses described in the literature. The synthesis of substituted 5-hydroxyisoquinolines is described, for example, in Heterocyclic Compounds, Vol. 38, Part 3, E. M. Coppola, H. F. Schuster, eds., Wiley, 1995, p. 229ff, and in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 162ff.

Scheme 61 illustrates methods for the preparation of substituted 5-hydroxyisoquinolines. As shown in Method 1, variously substituted 3-hydroxybenzaldehydes or 3-hydroxyphenyl ketones 61.1 are reacted with substituted or unsubstituted 2, 2-dialkoxyethylamines 61.2 in a procedure known as the Pomeranz-Fritsch reaction. The reactants are combined in a hydrocarbon solvent such as toluene at reflux temperature with azeotropic removal of water, to yield the imine product 61.3. The latter compound is then subjected to acid-catalyzed cyclization, for example as described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 164, to yield the substituted 5-hydroxyisoquinoline 61.4.

Scheme 61, Method 2 illustrates the preparation of variously substituted 5-hydroxyisoquinolines from the corresponding amino-substituted compounds. In this procedure, a suitably protected amino-substituted 5-hydroxyisoquinoline 61.5 is subjected to a diazotization reaction to afford the diazonium tetrafluoroborate, using the conditions described above in Scheme 57. The diazonium salt is then converted, as described above, into the corresponding hydroxy, mercapto or halo derivative 61.7.

Scheme 62 illustrates the preparation of the isoquinolinyl-5-oxyacetic acids 62.2 and the conversion of these compounds into the corresponding aminoacid derivatives 13.1. In this procedure, the 5-hydroxyisoquinoline substrate 62.1, in which the substituent A is either the group $\text{link-P(O)(OR}^1\text{)}_2$, or a precursor group thereto, such as [OH], [SH], [NH₂], Br, etc, as described herein, is converted into the corresponding aryloxyacetic acid 62.2. The procedures

employed for this transformation are the same as those described above, (Scheme 50) for the conversion of 2,6-dimethoxyphenol derivatives into the corresponding phenoxyacetic acids. The product 62.2 is then transformed, as described above, (Scheme 57) into the aminoacid derivative 13.1.

- 5 Schemes 63 - 65 illustrate the preparation of 5-hydroxyisoquinoline derivatives incorporating phosphonate substituents. The quinolinol products are then converted, as described above, into analogs of the aminoacid derivative 13.1.

- Scheme 63 illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a
10 phosphonate substituent is attached by means of an amide bond. In this procedure, an amino-substituted 5-hydroxyisoquinoline 63.1 is reacted with a dialkyl carboxyalkyl phosphonate 63.2 to afford the amide 63.3. The reaction is effected as described above for the preparation of the amides 1.3 and 1.6.

- For example, 8-amino-5-hydroxyisoquinoline 63.4, the preparation of which is described in
15 Syn. Comm., 1986, 16, 1557, is reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl 2-carboxyethyl phosphonate 63.5 (Epsilon) and dicyclohexyl carbodiimide, to produce the amide 63.6.

- Using the same procedures, but employing, in place of the 8-amino quinolinol 63.4, different
aminoquinolinols 63.1, and/or different dialkyl carboxyalkyl phosphonates 63.2, the
20 corresponding products 63.3 are obtained.

- Scheme 64 illustrates the preparation of 5-hydroxyisoquinoline derivatives in which a
phosphonate substituent is attached by means of a carbon link or a carbon and a heteroatom
link. In this procedure, a methyl-substituted 5-hydroxyisoquinoline 64.1 is protected, and the
25 product 64.2 is reacted with a free radical brominating agent, for example N-bromosuccinimide, as described in Chem. Rev., 63, 21, 1963, to afford the bromomethyl derivative 64.3. The latter compound is reacted with a trialkyl phosphite (R^1O)₃P under the conditions of the Arbuzov reaction, as described in Scheme 55, to yield the phosphonate 64.4; deprotection then affords the phenol 64.5.

- 30 Alternatively, the protected bromomethyl derivative 64.3 is reacted with a dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonate 64.6, to afford the alkylation product 64.7. The displacement reaction is conducted in a polar organic solvent such as dimethyl formamide,

acetonitrile and the like, in the presence of a base such as sodium hydride or lithium hexamethyldisilazide, for substrates in which X is O, or potassium carbonate for substrates in which X is S or N. The protecting group is then removed from the product 64.7 to yield the phenolic product 64.8.

- 5 For example, 5-hydroxy-1-methylisoquinoline 64.9, prepared as described in J. Med. Chem., 1968, 11, 700, is reacted with acetic anhydride in pyridine to afford 5-acetoxy-1-methylisoquinoline 64.10. The latter compound is reacted with N-bromosuccinimide in refluxing ethyl acetate to yield 5-acetoxy-1-bromomethylisoquinoline 64.11. The product is then reacted with five molar equivalents of a trialkyl phosphite at 120° to give the phosphonate product 64.12. The acetoxy group is hydrolyzed by reaction with sodium bicarbonate in aqueous methanol as described in J. Am. Chem. Soc., 93, 746, 1971, to produce the phenol 64.13.

Using the above procedures, but employing, in place of 5-hydroxy-1-methylisoquinoline 64.9, different hydroxymethylisoquinolines 64.1, the corresponding products 64.5 are obtained.

- 15 As a further illustration of the method of Scheme 64, as shown in Example 2, 5-hydroxy-3-methylisoquinoline 64.14, prepared as described in J. Med. Chem., 1998, 41, 4062, is reacted with one molar equivalent of tert. butyl chlorodimethylsilane and imidazole in dichloromethane to yield the silyl ether 64.15. The product is brominated, as described above, to afford 3-bromomethyl-5-tert. butyldimethylsilyloxyisoquinoline 64.16. The bromomethyl compound is then reacted in dimethylformamide at 60° with one molar equivalent of a dialkyl mercaptoethyl phosphonate 64.17, prepared as described in Zh. Obschei. Khim., 1973, 43, 2364, and potassium carbonate, to give the thioether product 64.18; deprotection, for example by treatment with 1M tetrabutylammonium fluoride in tetrahydrofuran, then yields the phenol 64.19.

- 25 Using the above procedures, but employing, in place of 5-hydroxy-3-methylisoquinoline 64.11, different hydroxymethylisoquinolines 64.1, and/or different hetero-substituted alkyl phosphonates 64.6, the corresponding products 64.8 are obtained.

- 30 Scheme 65 illustrates the preparation of 5-hydroxyisoquinoline derivatives incorporating a phosphonate moiety attached by means of a heteroatom and an alkylene chain. In this procedure, the phenolic hydroxyl group of 5-hydroxyisoquinolin-1-one 65.1 (Acros) is protected. The protection of phenolic hydroxyl groups is described, for example, in Protective

Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 143ff. The product 65.2 is then converted into the bromo analog 65.3, for example by reaction with phosphorus oxybromide, as described in Heterocyclic Compounds, Vol. 38, Part 2, E. M. Coppola, H. F. Schuster, eds., Wiley, 1995, p. 13ff. The bromo compound is then
5 reacted with a dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonate 65.4, to afford the displacement product 65.5. The displacement reaction of 2-haloisoquinolines with nucleophiles to produce ethers, thioethers and amines is described in Heterocyclic Chemistry, by T. L. Gilchrist, Longman, 1992, p. 165. The reaction is conducted in an organic solvent such as dimethylformamide, toluene and the like, in the presence of a base such as sodium
10 hydride or potassium carbonate. The phenolic hydroxyl group is then deprotected to yield the phenol 65.6.

For example, 5-hydroxyisoquinolin-1-one 65.1 is reacted with one molar equivalent of benzoyl chloride in pyridine to afford the ester 65.7. The latter compound is treated with phosphorus oxybromide in refluxing toluene to produce the 5-benzoyloxy-1-bromoisquinoline 65.8. This
15 material is reacted with a dialkyl 3-hydroxypropyl phosphonate 65.9, prepared as described in Zh. Obschei. Khim., 1974, 44, 1834, and sodium hydride in tetrahydrofuran to prepare the ether product 65.10. Deprotection, for example by reaction with aqueous alcoholic sodium bicarbonate, then yields the phenol 65.11.

Using the above procedures, but employing, in place of a dialkyl 3-hydroxypropyl
20 phosphonate 65.9, different dialkyl hydroxy, mercapto or amino-substituted alkyl phosphonates 65.4, the corresponding products 65.6 are obtained.

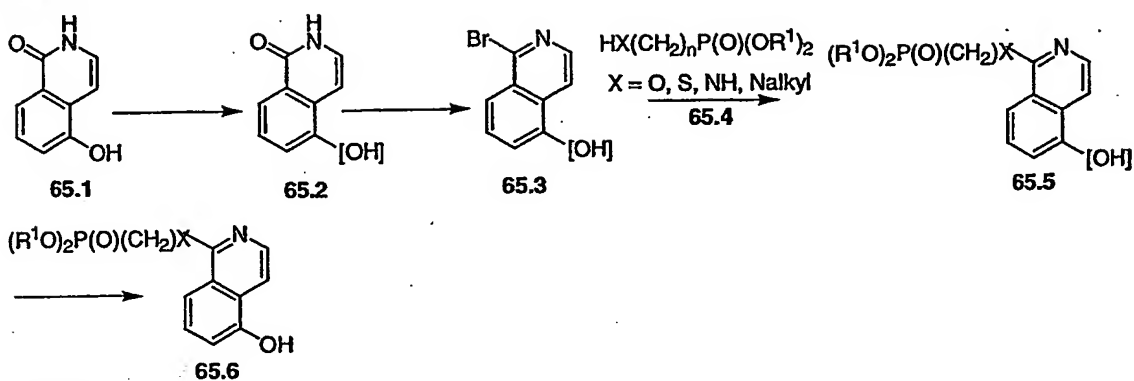
Scheme 66 described the preparation of 5-hydroxyisoquinolines in which a phosphonate substituent is attached by means of a saturated or unsaturated alkylene chain. In this
25 procedure, a bromo-substituted 5-hydroxyisoquinoline 66.1 is protected, as described above. The product 66.2 is coupled, in the presence of a palladium catalyst, with a dialkyl alkenyl phosphonate 66.3. The coupling of aryl bromides and alkenes is described above (Scheme 52). The product 66.4 is then deprotected to yield the phenol 66.5. Optionally, the compound 66.5 is reduced, for example by treatment with diimide or diborane, to afford the saturated analog
30 66.6.

For example, 5-hydroxyisoquinoline 66.7 is reacted with bromine in carbon tetrachloride to afford 8-bromo-5-hydroxyisoquinoline 66.8. The product is reacted with acetic anhydride in

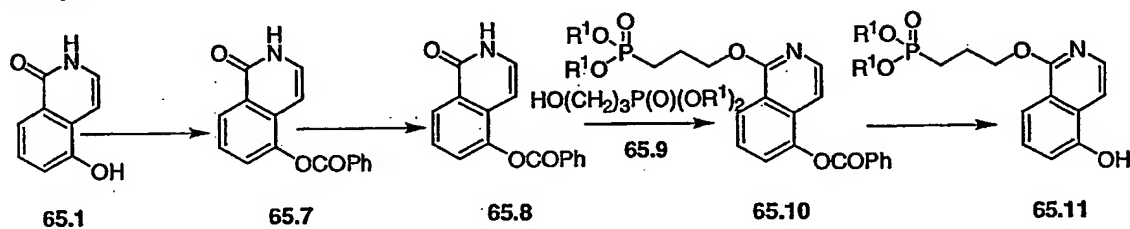
- pyridine to give 5-acetoxy-8-bromoisoquinoline **66.9**. The latter compound is coupled with a dialkyl propenyl phosphonate **66.10** (Aldrich) in the presence of ca. 3 mol % of bis(triphenylphosphine) palladium(II) chloride and triethylamine, in dimethylformamide at ca. 60°, to produce the coupled product **66.11**. The acetyl protecting group is then removed by
- 5 reaction with dilute aqueous methanolic ammonia, as described in J. Chem. Soc., 2137, 1964, to afford the phenol **66.12**. The product is optionally reduced to yield the saturated analog **66.13**. The reduction reaction is effected chemically, for example by the use of diimide or diborane, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 5, or catalytically.
- 10 Using the above procedures, but employing, in place of 8-bromo-5-hydroxyisoquinoline **66.8**, different bromo-substituted 5-hydroxyisoquinolines **66.1**, and/or different dialkyl alkenyl phosphonates **66.3**, the corresponding products **66.5** and **66.6** are obtained.

Scheme 65

Method

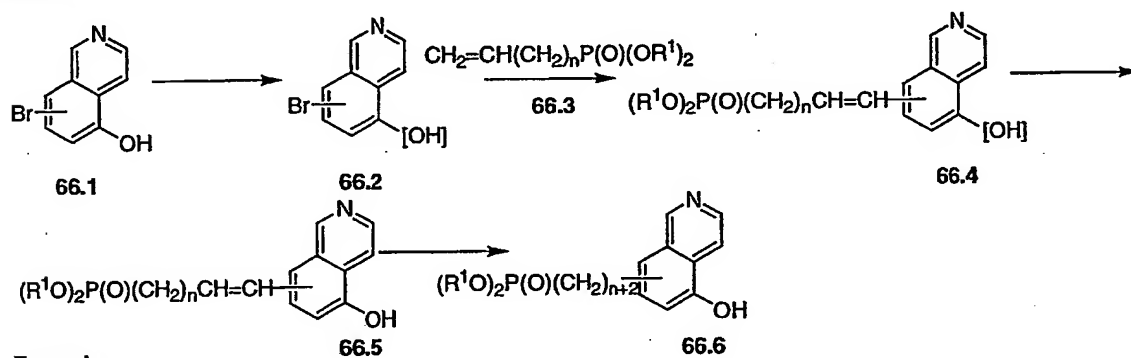


Example

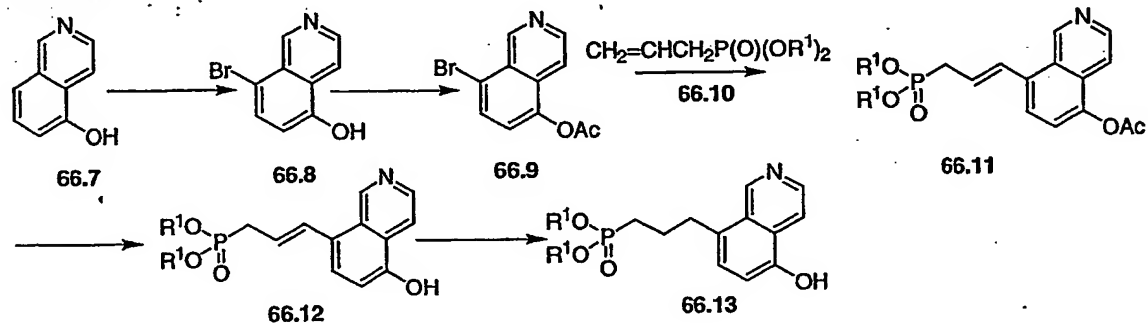


Scheme 66

Method



Example



Preparation of phenylalanine derivatives 17.1 incorporating phosphonate moieties.

Schemes 67 - 71 illustrate the preparation of phosphonate-containing phenylalanine derivatives 17.1 which are employed in the preparation of the intermediate phosphonate esters 5.

Scheme 67 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of a heteroatom and an alkylene chain. The compounds are obtained by means of alkylation or condensation reactions of hydroxy or mercapto-substituted phenylalanine derivatives 67.1.

In this procedure, a hydroxy or mercapto-substituted phenylalanine is converted into the benzyl ester 67.2. The conversion of carboxylic acids into esters is described for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 966. The conversion can be effected by means of an acid-catalyzed reaction between the carboxylic acid and benzyl alcohol, or by means of a base-catalyzed reaction between the carboxylic acid and a benzyl halide, for example benzyl chloride. The hydroxyl or mercapto substituent present in the benzyl ester 67.2 is then protected. Protection methods for phenols and thiols are

described respectively, for example, in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p 10, p 277. For example, suitable protecting groups for phenols and thiophenols include tert-butyldimethylsilyl or tert-butyldiphenylsilyl. Thiophenols may also be protected as S-adamantyl groups, as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 289 The protected hydroxy- or mercapto ester 67.3 is then converted into the BOC derivative 67.4. The protecting group present on the O or S substituent is then removed. Removal of O or S protecting groups is described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p10, p 277. For example, silyl protecting groups are removed by treatment with tetrabutylammonium fluoride and the like, in a solvent such as tetrahydrofuran at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972. S-Adamantyl groups can be removed by treatment with mercuric trifluoroacetate in acetic acid, as described in Chem. Pharm. Bull., 26, 1576, 1978.

The resultant phenol or thiophenol 67.5 is then reacted under various conditions to provide protected phenylalanine derivatives 67.9, 67.10 or 67.11, incorporating phosphonate moieties attached by means of a heteroatom and an alkylene chain.

In this step, the phenol or thiophenol 67.5 is reacted with a dialkyl bromoalkyl phosphonate 67.6 to afford the ether or thioether product 67.9. The alkylation reaction is effected in the

presence of an organic or inorganic base, such as, for example, diazabicyclononene, cesium carbonate or potassium carbonate, The reaction is performed at from ambient temperature to ca. 80°, in a polar organic solvent such as dimethylformamide or acetonitrile, to afford the ether or thioether product 67.9. Deprotection of the benzyl ester group, for example by means of catalytic hydrogenation over a palladium catalyst, then yields the carboxylic acid 67.12. The benzyl esters 67.10 and 67.11, the preparation of which is described above, are similarly deprotected to produce the corresponding carboxylic acids.

For example, as illustrated in Scheme 67, Example 1, a hydroxy-substituted phenylalanine derivative such as tyrosine, 67.13 is converted, as described above, into the benzyl ester 67.14.

10 The latter compound is then reacted with one molar equivalent of chloro tert-butyltrimethylsilane, in the presence of a base such as imidazole, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford the silyl ether 67.15. This compound is then converted, as described above, into the BOC derivative 67.16. The silyl protecting group is removed by treatment of the silyl ether 67.16 with a tetrahydrofuran solution of tetrabutyl ammonium fluoride at ambient temperature, as described in J. Am. Chem. Soc., 94, 6190, 1972, to afford 15 the phenol 67.17. The latter compound is then reacted in dimethylformamide at ca. 60°, with one molar equivalent of a dialkyl 3-bromopropyl phosphonate 67.18 (Aldrich), in the presence of cesium carbonate, to afford the alkylated product 67.19. Debenzylation then produces the carboxylic acid 67.20.

20 Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 67.13, different hydroxy or thio-substituted phenylalanine derivatives 67.1, and/or different bromoalkyl phosphonates 67.6, the corresponding ether or thioether products 67.12 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 67.5 25 is reacted with a dialkyl hydroxymethyl phosphonate 67.7 under the conditions of the Mitsunobu reaction, to afford the ether or thioether compounds 67.10. The preparation of aromatic ethers by means of the Mitsunobu reaction is described, for example, in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p 448, and in Advanced Organic Chemistry, Part B, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 153-4. The phenol or thiophenol and the alcohol component are reacted together in an aprotic 30 solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products 67.10.

For example, as shown in Scheme 67, Example 2, 3-mercaptophenylalanine 67.21, prepared as described in WO 0036136, is converted, as described above, into the benzyl ester 67.22. The resultant ester is then reacted in tetrahydrofuran solution with one molar equivalent of 4-methoxybenzyl chloride in the presence of ammonium hydroxide, as described in Bull. Chem. Soc. Jpn., 37, 433, 1974, to afford the 4-methoxybenzyl thioether 67.23. This compound is then converted, as described above for the preparation of the compound 67.4, into the BOC-protected derivative 67.24. The 4-methoxybenzyl group is then removed by the reaction of the thioether 67.24 with mercuric trifluoroacetate and anisole in trifluoroacetic acid, as described in J. Org. Chem., 52, 4420, 1987, to afford the thiol 67.25. The latter compound is reacted, under the conditions of the Mitsunobu reaction, with a dialkyl hydroxymethyl phosphonate 67.7, diethylazodicarboxylate and triphenylphosphine, for example as described in Synthesis, 4, 327, 1998, to yield the thioether product 67.26. The benzyl ester protecting group is then removed to afford the carboxylic acid 67.27.

Using the above procedures, but employing, in place of the mercapto-substituted phenylalanine derivative 67.21, different hydroxy or mercapto-substituted phenylalanines 67.1, and/or different dialkyl hydroxymethyl phosphonates 67.7, the corresponding products 67.10 are obtained.

Alternatively, the hydroxy or mercapto-substituted tribenzylated phenylalanine derivative 67.5 is reacted with an activated derivative of a dialkyl hydroxymethylphosphonate 67.8 in which Lv is a leaving group. The components are reacted together in a polar aprotic solvent such as, for example, dimethylformamide or dioxan, in the presence of an organic or inorganic base such as triethylamine or cesium carbonate, to afford the ether or thioether products 67.11.

For example, as illustrated in Scheme 67, Example 3, 3-hydroxyphenylalanine 67.28 (Fluka) is converted, using the procedures described above, into the protected compound 67.29. The latter compound is reacted, in dimethylformamide at ca. 50°, in the presence of potassium carbonate, with diethyl trifluoromethanesulfonyloxymethylphosphonate 67.30, prepared as described in Tet. Lett., 1986, 27, 1477, to afford the ether product 67.31. Debenzylation then produces the carboxylic acid 67.32.

Using the above procedures, but employing, in place of the hydroxy-substituted phenylalanine derivative 67.28, different hydroxy or mercapto-substituted phenylalanines 67.1, and/or different dialkyl trifluoromethanesulfonyloxymethylphosphonates 67.8, the corresponding products 67.11 are obtained.

Scheme 68 illustrates the preparation of phenylalanine derivatives incorporating phosphonate moieties attached to the phenyl ring by means of an alkylene chain incorporating a nitrogen atom. The compounds are obtained by means of a reductive alkylation reaction between a
5 formyl-substituted tribenzylated phenylalanine derivative 68.3 and a dialkyl aminoalkylphosphonate 68.4.

In this procedure, a hydroxymethyl-substituted phenylalanine 68.1 is converted, as described above, into the BOC protected benzyl ester 68.2. The latter compound is then oxidized to afford the corresponding aldehyde 68.3. The conversion of alcohols to aldehydes is described,
10 for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p 604ff. Typically, the alcohol is reacted with an oxidizing agent such as pyridinium chlorochromate, silver carbonate, or dimethyl sulfoxide/acetic anhydride, to afford the aldehyde product 68.3. For example, the carbinol 68.2 is reacted with phosgene, dimethyl sulfoxide and triethylamine, as described in *J. Org. Chem.*, 43, 2480, 1978, to yield the
15 aldehyde 68.3. This compound is reacted with a dialkyl aminoalkylphosphonate 68.4 in the presence of a suitable reducing agent to afford the amine product 68.5. The preparation of amines by means of reductive amination procedures is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, p 421, and in *Advanced Organic Chemistry, Part B*, by F.A. Carey and R. J. Sundberg, Plenum, 2001, p 269. In this
20 procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetrakisopropoxide, as described in *J. Org. Chem.*, 55, 2552, 1990. The benzyl protecting group is then removed to prepare the carboxylic acid 68.6.

For example, 3-(hydroxymethyl)-phenylalanine 68.7, prepared as described in *Acta Chem. Scand. Ser. B*, 1977, B31, 109, is converted, as described above, into the formylated derivative 68.8. This compound is then reacted with a dialkyl aminoethylphosphonate 68.9,
25 prepared as described in *J. Org. Chem.*, 200, 65, 676, in the presence of sodium cyanoborohydride, to produce the alkylated product 68.10, which is then deprotected to give
30 the carboxylic acid 68.11.

Using the above procedures, but employing, in place of 3-(hydroxymethyl)-phenylalanine 68.7, different hydroxymethyl phenylalanines 68.1, and/or different aminoalkyl phosphonates 68.4, the corresponding products 68.6 are obtained.

- 5 Scheme 69 depicts the preparation of phenylalanine derivatives in which a phosphonate moiety is attached directly to the phenyl ring. In this procedure, a bromo-substituted phenylalanine 69.1 is converted, as described above, (Scheme 68) into the protected derivative 69.2. The product is then coupled, in the presence of a palladium(0) catalyst, with a dialkyl phosphite 69.3 to produce the phosphonate ester 69.4. The preparation of arylphosphonates by means of
- 10 a coupling reaction between aryl bromides and dialkyl phosphites is described in J. Med. Chem., 35, 1371, 1992. The product is then deprotected to afford the carboxylic acid 69.5. For example, 3-bromophenylalanine 69.6, prepared as described in Pept. Res., 1990, 3, 176, is converted, as described above, (Scheme 68) into the protected compound 69.7. This compound is then reacted, in toluene solution at reflux, with diethyl phosphite 69.8,
- 15 triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in J. Med. Chem., 35, 1371, 1992, to afford the phosphonate product 69.9. Debenzylation then yields the carboxylic acid 69.10.

- Using the above procedures, but employing, in place of 3-bromophenylalanine 69.6, different bromophenylalanines 69.1, and/or different dialkylphosphites 69.3, the corresponding products
- 20 69.5 are obtained.

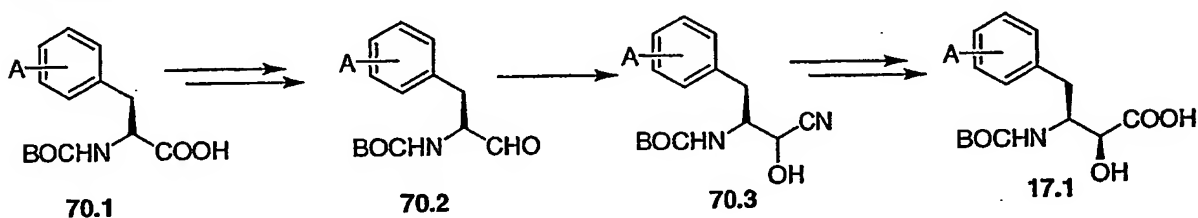
- Schemes 70 and 71 illustrate two methods for the conversion of the compounds 70.1, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives 17.1 which are employed in the preparation of
- 25 the intermediate phosphonate esters 5.

- As shown in Scheme 70, the BOC-protected phenylalanine derivative 70.1 is converted, using the procedures described above in Scheme 41, into the aldehyde 70.2. The aldehyde is then converted, via the cyanohydrin 70.3, into the homologated derivative 17.1. The reaction sequence and conditions employed are the same as shown in Scheme 41 for the conversion of
- 30 the BOC-protected aminoacid 41.1 into the homologated derivative 1.5.

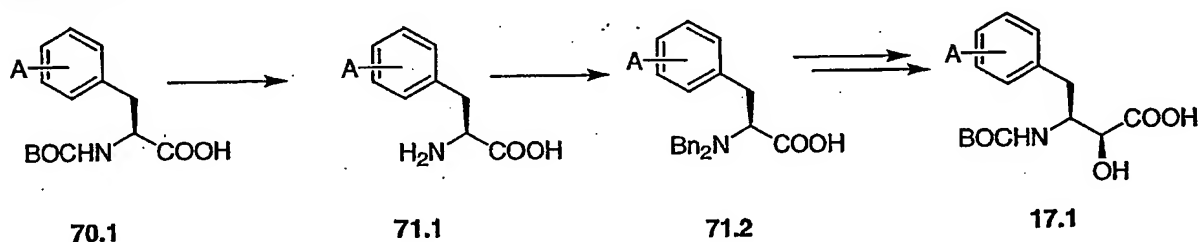
Alternatively, as illustrated in Scheme 71, the BOC-protected aminoacid 70.1 is deprotected to afford the amine 71.1. The product is then converted, as described in Scheme 42, into the

dibenzylated product 71.2. The latter compound is then transformed, using the sequence of reactions and conditions shown in Scheme 42 for the conversion of the dibenzylated aminoacid 42.1 into the hydroxyacid 1.5, into the homologated derivative 17.1.

Scheme 70



Scheme 71



5

Preparation of the phosphonate-containing thiophenol derivatives 19.1.

Schemes 72 - 83 describe the preparation of phosphonate-containing thiophenol derivatives 19.1 which are employed as described above (Schemes 19 and 20) in the preparation of the phosphonate ester intermediates 5 in which X is sulfur. Schemes 72 - 81 described the syntheses of the thiophenol components; Schemes 82 and 83 described methods for the incorporation of the thiophenols into the reactants 19.1.

15 Scheme 72 depicts the preparation of thiophenol derivatives in which the phosphonate moiety is attached directly to the phenyl ring. In this procedure, a halo-substituted thiophenol 72.1 is protected, as described above (Scheme 67) to afford the protected product 72.2. The product is then coupled, in the presence of a palladium catalyst, with a dialkyl phosphite 72.3, to afford the phosphonate ester 72.4. The preparation of arylphosphonates by the coupling of aryl

20 halides with dialkyl phosphites is described above, (Scheme 69). The thiol protecting group is then removed, as described above, to afford the thiol 72.5.

For example, 3-bromothiophenol 72.6 is converted into the 9-fluorenylmethyl (Fm) derivative 72.7 by reaction with 9-fluorenylmethyl chloride and diisopropylethylamine in dimethylformamide, as described in Int. J. Pept. Protein Res., 20, 434, 1982. The product is then reacted with a dialkyl phosphite 72.3, as described for the preparation of the phosphonate 5 69.4 (Scheme 69), to afford the phosphonate ester 72.8. The Fm protecting group is then removed by treatment of the product with piperidine in dimethylformamide at ambient temperature, as described in J. Chem. Soc., Chem. Comm., 1501, 1986, to give the thiol 72.9. Using the above procedures, but employing, in place of 3-bromothiophenol 72.6, different thiophenols 72.1, and/or different dialkyl phosphites 72.3, the corresponding products 72.5 are 10 obtained.

Scheme 73 illustrates an alternative method for obtaining thiophenols with a directly attached phosphonate group. In this procedure, a suitably protected halo-substituted thiophenol 73.2 is metallated, for example by reaction with magnesium or by transmetallation with an 15 alkylolithium reagent, to afford the metallated derivative 73.3. The latter compound is reacted with a halodialkyl phosphite 73.4 to afford the product 73.5; deprotection then affords the thiophenol 73.6

For example, 4-bromothiophenol 73.7 is converted into the S-triphenylmethyl (trityl) derivative 73.8, as described in Protective Groups in Organic Synthesis, by T. W. Greene and 20 P.G.M. Wuts, Wiley, 1991, pp. 287. The product is converted into the lithium derivative 73.9 by reaction with butyllithium in an ethereal solvent at low temperature, and the resulting lithio compound is reacted with a dialkyl chlorophosphite 73.10 to afford the phosphonate 73.11. Removal of the trityl group, for example by treatment with dilute hydrochloric acid in acetic acid, as described in J. Org. Chem., 31, 1118, 1966, then affords the thiol 73.12. 25 Using the above procedures, but employing, in place of the bromo compound 73.7, different halo compounds 73.1, and/or different halo dialkyl phosphites 73.4, there are obtained the corresponding thiols 73.6.

Scheme 74 illustrates the preparation of phosphonate-substituted thiophenols in which the 30 phosphonate group is attached by means of a one-carbon link. In this procedure, a suitably protected methyl-substituted thiophenol 74.1 is subjected to free-radical bromination to afford a bromomethyl product 74.2. This compound is reacted with a sodium dialkyl phosphite 74.3

or a trialkyl phosphite, to give the displacement or rearrangement product 74.4, which upon deprotection affords the thiophenol 74.5.

For example, 2-methylthiophenol 74.6 is protected by conversion to the benzoyl derivative 74.7, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M.

- 5 Wuts, Wiley, 1991, pp. 298. The product is reacted with N-bromosuccinimide in ethyl acetate to yield the bromomethyl product 74.8. This material is reacted with a sodium dialkyl phosphite 74.3, as described in J. Med. Chem., 35, 1371, 1992, to afford the product 74.9. Alternatively, the bromomethyl compound 74.8 is converted into the phosphonate 74.9 by means of the Arbuzov reaction, for example as described in Handb. Organophosphorus Chem.,
10 1992, 115. In this procedure, the bromomethyl compound 74.8 is heated with a trialkyl phosphate $P(OR^1)_3$ at ca. 100° to produce the phosphonate 74.9. Deprotection of the phosphonate 74.9, for example by treatment with aqueous ammonia, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiol 74.10.

- Using the above procedures, but employing, in place of the bromomethyl compound 74.8,
15 different bromomethyl compounds 74.2, there are obtained the corresponding thiols 74.5.

- Scheme 75 illustrates the preparation of thiophenols bearing a phosphonate group linked to the phenyl nucleus by oxygen or sulfur. In this procedure, a suitably protected hydroxy or thio-substituted thiophenol 75.1 is reacted with a dialkyl hydroxyalkylphosphonate 75.2 under
20 the conditions of the Mitsunobu reaction, for example as described in Org. React., 1992, 42, 335, to afford the coupled product 75.3. Deprotection then yields the O- or S-linked products 75.4.

- For example, the substrate 3-hydroxythiophenol, 75.5, is converted into the monotrityl ether 75.6, by reaction with one equivalent of trityl chloride, as described above. This compound is
25 reacted with diethyl azodicarboxylate, triphenyl phosphine and a dialkyl 1-hydroxymethyl phosphonate 75.7 in benzene, as described in Synthesis, 4, 327, 1998, to afford the ether compound 75.8. Removal of the trityl protecting group, as described above, then affords the thiophenol 75.9.

- Using the above procedures, but employing, in place of the phenol 75.5, different phenols or
30 thiophenols 75.1, there are obtained the corresponding thiols 75.4.

Scheme 76 illustrates the preparation of thiophenols 76.4 bearing a phosphonate group linked to the phenyl nucleus by oxygen, sulfur or nitrogen. In this procedure, a suitably protected O, S or N-substituted thiophenol 76.1 is reacted with an activated ester, for example the trifluoromethanesulfonate 76.2, of a dialkyl hydroxyalkyl phosphonate, to afford the coupled product 76.3. Deprotection then affords the thiol 76.4.

For example, 4-methylaminothiophenol 76.5 is reacted in dichloromethane solution with one equivalent of acetyl chloride and a base such as pyridine, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, pp. 298, to afford the S-acetyl product 76.6. This material is then reacted with a dialkyl trifluoromethanesulfonylmethyl phosphonate 76.7, the preparation of which is described in Tet. Lett., 1986, 27, 1477, to afford the displacement product 76.8. Preferably, equimolar amounts of the phosphonate 76.7 and the amine 76.6 are reacted together in an aprotic solvent such as dichloromethane, in the presence of a base such as 2,6-lutidine, at ambient temperatures, to afford the phosphonate product 76.8. Deprotection, for example by treatment with dilute aqueous sodium hydroxide for two minutes, as described in J. Am. Chem. Soc., 85, 1337, 1963, then affords the thiophenol 76.9.

Using the above procedures, but employing, in place of the thioamine 76.5, different phenols, thiophenols or amines 76.1, and/or different phosphonates 76.2, there are obtained the corresponding products 76.4.

Scheme 77 illustrates the preparation of phosphonate esters linked to a thiophenol nucleus by means of a heteroatom and a multiple-carbon chain, employing a nucleophilic displacement reaction on a dialkyl bromoalkyl phosphonate 77.2. In this procedure, a suitably protected hydroxy, thio or amino substituted thiophenol 77.1 is reacted with a dialkyl bromoalkyl phosphonate 77.2 to afford the product 77.3. Deprotection then affords the free thiophenol 77.4.

For example, 3-hydroxythiophenol 77.5 is converted into the S-trityl compound 77.6, as described above. This compound is then reacted with, for example, a dialkyl 4-bromobutyl phosphonate 77.7, the synthesis of which is described in Synthesis, 1994, 9, 909. The reaction is conducted in a dipolar aprotic solvent, for example dimethylformamide, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of

potassium iodide, at about 50°, to yield the ether product 77.8. Deprotection, as described above, then affords the thiol 77.9.

Using the above procedures, but employing, in place of the phenol 77.5, different phenols, thiophenols or amines 77.1, and/or different phosphonates 77.2, there are obtained the
5 corresponding products 77.4.

Scheme 78 depicts the preparation of phosphonate esters linked to a thiophenol nucleus by means of unsaturated and saturated carbon chains. The carbon chain linkage is formed by means of a palladium catalyzed Heck reaction, in which an olefinic phosphonate 78.2 is
10 coupled with an aromatic bromo compound 78.1. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in Advanced Organic Chemistry, by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12, 146, 1979. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as
15 tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product 78.3. Deprotection, or hydrogenation of the double bond followed by deprotection, affords respectively the unsaturated phosphonate 78.4, or the saturated analog 78.6.
20 For example, 3-bromothiophenol is converted into the S-Fm derivative 78.7, as described above, and this compound is reacted with a dialkyl 1-butenyl phosphonate 78.8, the preparation of which is described in J. Med. Chem., 1996, 39, 949, in the presence of a palladium (II) catalyst, for example, bis(triphenylphosphine) palladium (II) chloride, as described in J. Med. Chem, 1992, 35, 1371. The reaction is conducted in an aprotic dipolar
25 solvent such as, for example, dimethylformamide, in the presence of triethylamine, at about 100° to afford the coupled product 78.9. Deprotection, as described above, then affords the thiol 78.10. Optionally, the initially formed unsaturated phosphonate 78.9 is subjected to reduction, for example using diimide, as described above, to yield the saturated product 78.11, which upon deprotection affords the thiol 78.12.
30 Using the above procedures, but employing, in place of the bromo compound 78.7, different bromo compounds 78.1, and/or different phosphonates 78.2, there are obtained the corresponding products 78.4 and 78.6

Scheme 79 illustrates the preparation of an aryl-linked phosphonate ester 79.4 by means of a palladium(0) or palladium(II) catalyzed coupling reaction between a bromobenzene and a phenylboronic acid, as described in Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 57. The sulfur-substituted phenylboronic acid 79.1 is obtained by means of a metallation-boronation sequence applied to a protected bromo-substituted thiophenol, for example as described in J. Org. Chem., 49, 5237, 1984. A coupling reaction then affords the diaryl product 79.3 which is deprotected to yield the thiol 79.4.

For example, protection of 4-bromothiophenol by reaction with tert-butylchlorodimethylsilane, in the presence of a base such as imidazole, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 297, followed by metallation with butyllithium and boronation, as described in J. Organomet. Chem., 1999, 581, 82, affords the boronate 79.5. This material is reacted with a dialkyl 4-bromophenylphosphonate 79.6, the preparation of which is described in J. Chem. Soc., Perkin Trans., 1977, 2, 789, in the presence of tetrakis(triphenylphosphine) palladium (0) and an inorganic base such as sodium carbonate, to afford the coupled product 79.7. Deprotection, for example by the use of tetrabutylammonium fluoride in anhydrous tetrahydrofuran, then yields the thiol 79.8.

Using the above procedures, but employing, in place of the boronate 79.5, different boronates 79.1, and/or different phosphonates 79.2, there are obtained the corresponding products 79.4.

Scheme 80 depicts the preparation of dialkyl phosphonates in which the phosphonate moiety is linked to the thiophenyl group by means of a chain which incorporates an aromatic or heteroaromatic ring. In this procedure, a suitably protected O, S or N-substituted thiophenol 80.1 is reacted with a dialkyl bromomethyl-substituted aryl or heteroarylphosphonate 80.2, prepared, for example, by means of an Arbuzov reaction between equimolar amounts of a bis(bromo-methyl) substituted aromatic compound and a trialkyl phosphite. The reaction product 80.3 is then deprotected to afford the thiol 80.4. For example, 1,4-dimercaptobenzene is converted into the monobenzoyl ester 80.5 by reaction with one molar equivalent of benzoyl chloride, in the presence of a base such as pyridine. The monoprotected thiol 80.5 is then reacted with a dialkyl 4-(bromomethyl)phenylphosphonate, 80.6, the preparation of which is described in Tetrahedron, 1998, 54, 9341. The reaction is conducted in a solvent such as dimethylformamide, in the presence of a base such as potassium carbonate, at about 50°. The

thioether product **80.7** thus obtained is deprotected, as described above, to afford the thiol **80.8**.

Using the above procedures, but employing, in place of the thiophenol **80.5**, different phenols, thiophenols or amines **80.1**, and/or different phosphonates **80.2**, there are obtained the
5 corresponding products **80.4**.

Scheme **81** illustrates the preparation of phosphonate-containing thiophenols in which the attached phosphonate chain forms a ring with the thiophenol moiety.

In this procedure, a suitably protected thiophenol **81.1**, for example an indoline (in which X-Y is $(CH_2)_2$), an indole (X-Y is $CH=CH$) or a tetrahydroquinoline (X-Y is $(CH_2)_3$) is reacted
10 with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate **81.2**, in the presence of an organic or inorganic base, in a polar aprotic solvent such as, for example, dimethylformamide, to afford the phosphonate ester **81.3**. Deprotection, as described above, then affords the thiol **81.4**. The preparation of thio-substituted indolines is described in EP 209751. Thio-substituted
15 indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding hydroxy-substituted compounds, for example by thermal rearrangement of the dimethylthiocarbamoyl esters, as described in J. Org. Chem., 31, 3980, 1966. The preparation of hydroxy-substituted indoles is described in Syn., 1994, 10, 1018; preparation of hydroxy-substituted indolines is described in Tet. Lett., 1986, 27, 4565, and the preparation of
20 hydroxy-substituted tetrahydroquinolines is described in J. Het. Chem., 1991, 28, 1517, and in J. Med. Chem., 1979, 22, 599. Thio-substituted indoles, indolines and tetrahydroquinolines can also be obtained from the corresponding amino and bromo compounds, respectively by diazotization, as described in Sulfur Letters, 2000, 24, 123, or by reaction of the derived organolithium or magnesium derivative with sulfur, as described in Comprehensive Organic
25 Functional Group Preparations, A. R. Katritzky et al, eds, Pergamon, 1995, Vol. 2, p 707. For example, 2,3-dihydro-1H-indole-5-thiol, **81.5**, the preparation of which is described in EP 209751, is converted into the benzoyl ester **81.6**, as described above, and the ester is then reacted with the trifluoromethanesulfonate **81.7**, using the conditions described above for the preparation of the phosphonate **76.8**, (Scheme 76), to yield the phosphonate **81.8**.
30 Deprotection, for example by reaction with dilute aqueous ammonia, as described above, then affords the thiol **81.9**.

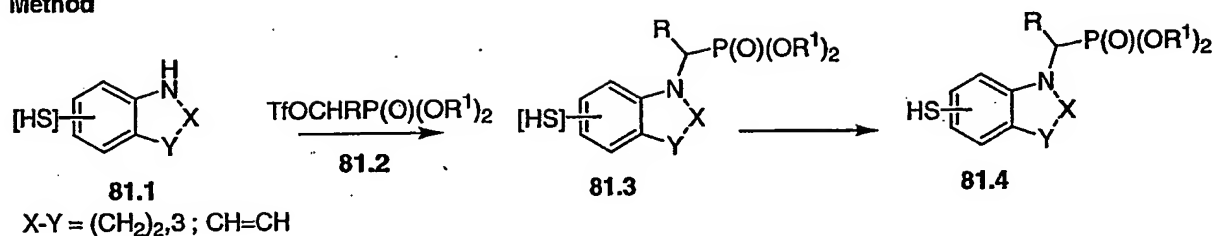
Using the above procedures, but employing, in place of the thiol **81.5**, different thiols **81.1**, and/or different triflates **81.2**, there are obtained the corresponding products **81.4**.

Schemes **82** and **83** illustrate alternative methods for the conversion of the thiophenols **82.1**, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, prepared as described above, (Schemes **72 – 81**) in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, into the homologated derivatives **19.1** which are employed in the preparation of the intermediate phosphonate esters **5** in which X is sulfur.

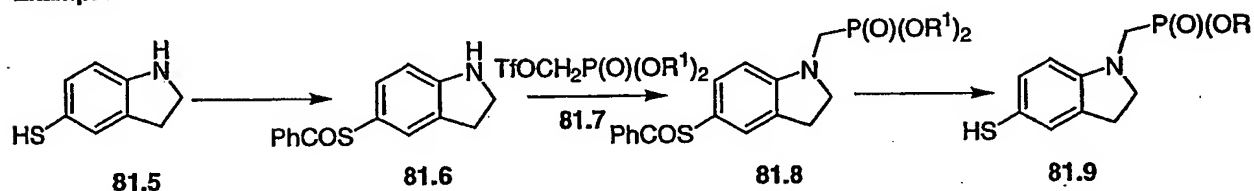
- 10 As shown in Scheme **82**, the thiophenol **82.1** is reacted with the mesylate ester **43.2**, using the conditions described above for the preparation of the thioether **43.4**, to afford the corresponding thioether **82.2**. The latter compound is then transformed, using the same sequence of reactions and reaction conditions described above (Scheme **43**) for the conversion of the thioether **43.4** into the hydroxyacid **3.1**, into the hydroxyacid **19.1**.
- 15 Alternatively, as shown in Scheme **83**, the aldehyde **82.3** is converted, as shown in Scheme **44**, into the diol **83.1**. The latter compound is then converted, as shown in Scheme **44** into the hydroxyacid **19.1**.

Scheme 81

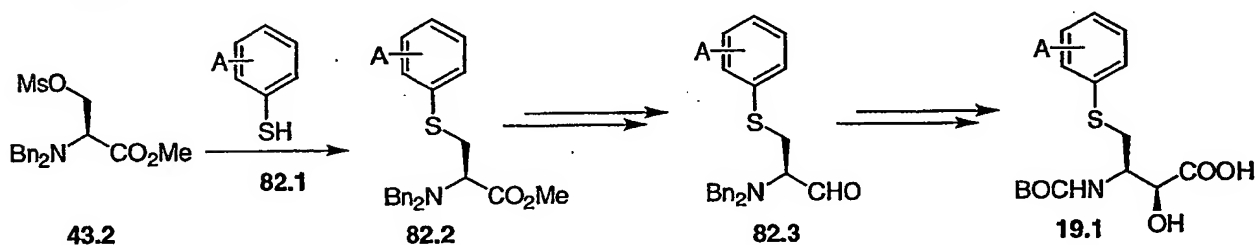
Method



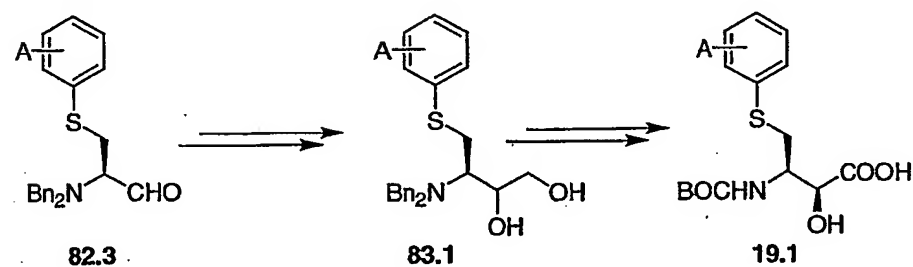
Example



Scheme 82



Scheme 83



Preparation of tert-butylamine derivatives 25.1 incorporating phosphonate groups.

- 5 Schemes 84 – 87 illustrate the preparation of the tert. butylamine derivatives 25.1 in which the substituent A is either the group link $\text{P(O)}(\text{OR}^1)_2$ or a precursor thereto, such as $[\text{OH}]$, $[\text{SH}]$, Br etc, which are employed in the preparation of the intermediate phosphonate esters 7.

- 10 Scheme 84 describes the preparation of tert-butylamines in which the phosphonate moiety is directly attached to the tert-butyl group. A suitably protected 2,2-dimethyl-2-aminoethyl

bromide 84.1 is reacted with a trialkyl phosphite 84.2, under the conditions of the Arbuzov reaction, as described above, to afford the phosphonate 84.3, which is then deprotected as described previously to give 84.4

For example, the cbz derivative of 2,2-dimethyl-2-aminoethyl bromide 84.6, is heated with a trialkyl phosphite at ca 150° to afford the product 84.7. Deprotection, as previously described, then affords the free amine 84.8.

Using the above procedures, but employing different trisubstituted phosphites, there are obtained the corresponding amines 84.4.

10 Scheme 85 illustrates the preparation of phosphonate esters attached to the tert butylamine by means of a heteroatom and a carbon chain. An optionally protected alcohol or thiol 85.1 is reacted with a bromoalkylphosphonate 85.2, to afford the displacement product 85.3.

Deprotection, if needed, then yields the amine 85.4.

For example, the cbz derivative of 2-amino-2,2-dimethylethanol 85.5 is reacted with a dialkyl 4-bromobutyl phosphonate 85.6, prepared as described in Synthesis, 1994, 9, 909, in dimethylformamide containing potassium carbonate and a catalytic amount of potassium iodide, at ca 60° to afford the phosphonate 85.7. Deprotection, by hydrogenation over a palladium catalyst, then affords the free amine 85.8.

Using the above procedures, but employing different alcohols or thiols 85.1, and/or different bromoalkylphosphonates 85.2, there are obtained the corresponding ether and thioether products 85.4.

Scheme 86 describes the preparation of carbon-linked tert. butylamine phosphonate derivatives, in which the carbon chain can be unsaturated or saturated.

25 In the procedure, a terminal acetylenic derivative of tert-butylamine 86.1 is reacted, under basic conditions, with a dialkyl chlorophosphite 86.2, to afford the acetylenic phosphonate 86.3. The coupled product 86.3 is deprotected to afford the amine 86.4. Partial or complete catalytic hydrogenation of this compound affords the olefinic and saturated products 86.5 and 86.6 respectively.

30 For example, 2-amino-2-methylprop-1-yne 86.7, the preparation of which is described in WO 9320804, is converted into the N-phthalimido derivative 86.8, by reaction with phthalic anhydride, as described in Protective Groups in Organic Synthesis, by T. W. Greene and

- P.G.M. Wuts, Wiley, 1991, pp. 358. This compound is reacted with lithium diisopropylamide in tetrahydrofuran at -78°. The resultant anion is then reacted with a dialkyl chlorophosphite 86.2 to afford the phosphonate 86.9. Deprotection, for example by treatment with hydrazine, as described in J. Org. Chem., 43, 2320, 1978, then affords the free amine 86.10. Partial
- 5 catalytic hydrogenation, for example using Lindlar catalyst, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 1, p 566, produces the olefinic phosphonate 86.11, and conventional catalytic hydrogenation, as described in Organic Functional Group Preparations, by S.R. Sandler and W. Karo, Academic Press, 1968, p. 3. for example using 5% palladium on carbon as catalyst, affords the saturated phosphonate 86.12.
- 10 Using the above procedures, but employing different acetylenic amines 86.1, and/or different dialkyl halophosphites, there are obtained the corresponding products 86.4, 86.5 and 86.6.

Scheme 87 illustrates the preparation of a tert butylamine phosphonate in which the phosphonate moiety is attached by means of a cyclic amine.

- 15 In this method, an aminoethyl-substituted cyclic amine 87.1 is reacted with a limited amount of a bromoalkyl phosphonate 87.2, using, for example, the conditions described above (Scheme 78) to afford the displacement product 87.3.

For example, 3-(1-amino-1-methyl)ethylpyrrolidine 87.4, the preparation of which is described in Chem. Pharm. Bull., 1994, 42, 1442, is reacted with one molar equivalent of a dialkyl 4-

20 bromobutyl phosphonate 87.5, prepared as described in Synthesis, 1994, 9, 909, to afford the displacement product 87.6.

Using the above procedures, but employing, in place of 3-(1-amino-1-methyl)ethylpyrrolidine 87.4, different cyclic amines 87.1, and/or different bromoalkylphosphonates 87.2, there are obtained the corresponding products 87.3.

25

Method

Example

Scheme 87

Method

Example

Preparation of phosphonate-containing methyl-substituted benzylamines 29.1.

- 5 Schemes 88 – 90 illustrate the preparation of phosphonate-containing 2-methyl and 2,6-dimethylbenzylamines 29.1 in which the substituent A is either the group link $\text{P}(\text{O})(\text{OR}^1)_2$ or a precursor thereto, such as $[\text{OH}]$, $[\text{SH}]$, Br etc, which are employed in the preparation of the phosphonate ester intermediates 8, as described in Schemes 29 – 32. A number of variously substituted 2-methyl and 2,6-dimethylbenzylamines are commercially available or have published syntheses. In addition, substituted benzylamines are prepared by various methods

known to those skilled in the art. For example, substituted benzylamines are obtained by reduction of the correspondingly substituted benzamides, for example by the use of diborane or lithium aluminum hydride, as described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, 1989, p. 432ff.

5

Scheme 88 depicts the preparation of 2-methyl or 2,6-dimethylbenzylamines incorporating a phosphonate moiety directly attached to the benzene ring, or attached by means of a saturated or unsaturated alkylene chain. In this procedure, a bromo-substituted 2-methyl or 2,6-dimethylbenzylamine 88.1 is protected to produce the analog 88.2. The protection of amines is described, for example, in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 309ff. For example, the amine 88.1 is protected as an amide or carbamate derivative. The protected amine is then reacted with a dialkyl phosphite 88.3, in the presence of a palladium catalyst, as described above (Scheme 69) to afford the phosphonate product 88.4. Deprotection then affords the free amine 88.5.

10

Alternatively, the protected bromo-substituted benzylamine 88.2 is coupled with a dialkyl alkenyl phosphonate 88.6, using the conditions of the Heck reaction, as described above, (Scheme 59) to afford the alkenyl product 88.7. The amino protecting group is then removed to yield the free amine 88.8. Optionally, the olefinic double bond is reduced, for example by the use of diborane or diimide, or by means of catalytic hydrogenation, as described above (Scheme 59) to produce the saturated analog 88.9.

15

20

For example, 4-bromo-2,6-dimethylbenzylamine 88.10, (Trans World Chemicals) is converted into the BOC derivative 88.11, as described above, and the product is coupled with a dialkyl phosphite 88.3, in the presence of triethylamine and tetrakis(triphenylphosphine)palladium(0), as described in *J. Med. Chem.*, 35, 1371, 1992, to yield the phosphonate ester 88.12.

25

Deprotection, for example by treatment with trifluoroacetic acid, then produces the free amine 88.13.

Using the above procedures, but employing, in place of 4-bromo-2,6-dimethylbenzylamine 88.10, different bromobenzylamines 88.1, the corresponding products 88.5 are obtained.

30

As an additional example of the methods of Scheme 88, 4-bromo-2-methylbenzylamine 88.14 (Trans World Chemicals) is converted into the BOC derivative 88.15. The latter compound is then reacted with a dialkyl vinylphosphonate 88.16, (Aldrich) in the presence of 2 mol % of tetrakis(triphenylphosphine)palladium and triethylamine, to afford the coupled product 88.17.

Deprotection then affords the amine 88.18, and reduction of the latter compound with diimide gives the saturated analog 88.19.

Using the above procedures, but employing, in place of 4-bromo-2-methylbenzylamine 88.14, different bromobenzylamines 88.1, and/or different alkenyl phosphonates 88.6, the
5 corresponding products 88.8 and 88.9 are obtained.

Scheme 89 depicts the preparation of 2-methyl or 2,6-dimethylbenzylamines incorporating a phosphonate moiety attached to the benzene ring by means of an amide linkage. In this procedure, the amino group of a carboxy-substituted 2-methyl or 2,6-dimethylbenzylamine
10 89.1 is protected to yield the product 89.2. The latter compound is then reacted with a dialkyl aminoalkyl phosphonate 89.3 to afford the amide 89.4. The reaction is performed as described above for the preparation of the amides 1.3 and 1.6. The amine protecting group is then removed to give the free amine 89.5.

For example, 4-carboxy-2-methylbenzylamine 89.6, prepared as described in Chem. Pharm.
15 Bull., 1979, 21, 3039, is converted into the BOC derivative 89.7. This material is then reacted in tetrahydrofuran solution with one molar equivalent of a dialkyl aminoethyl phosphonate 89.8, in the presence of dicyclohexylcarbodiimide and hydroxybenzotriazole, to produce the amide 89.9. Deprotection, for example by reaction with methanesulfonic acid in acetonitrile, then yields the amine 89.10.

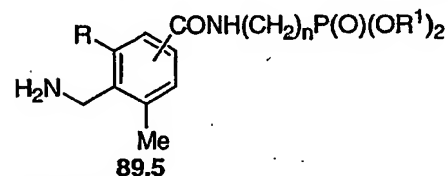
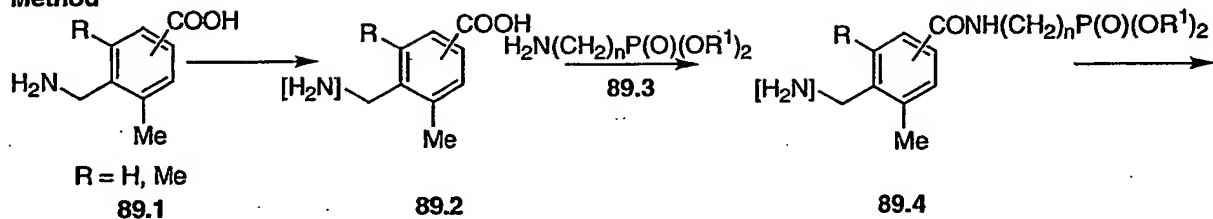
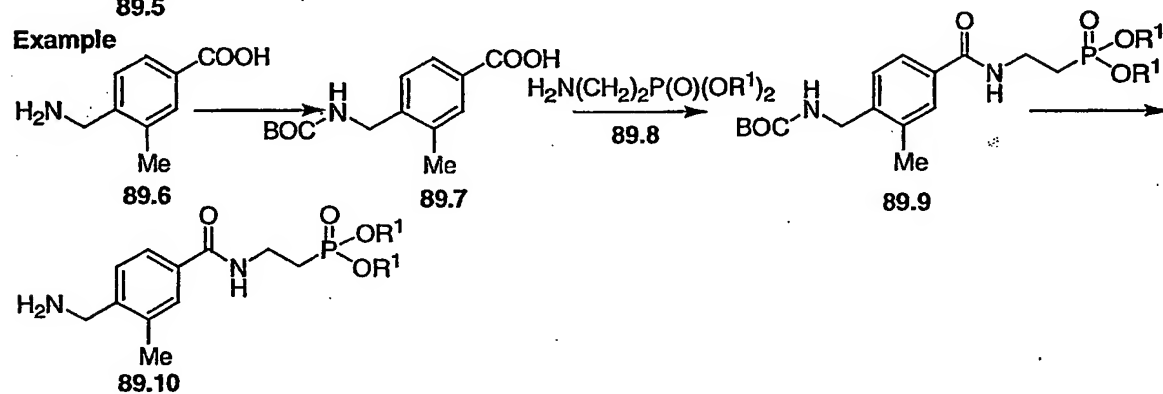
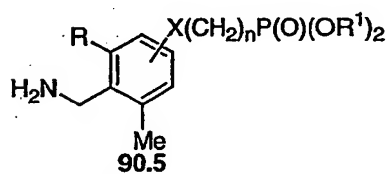
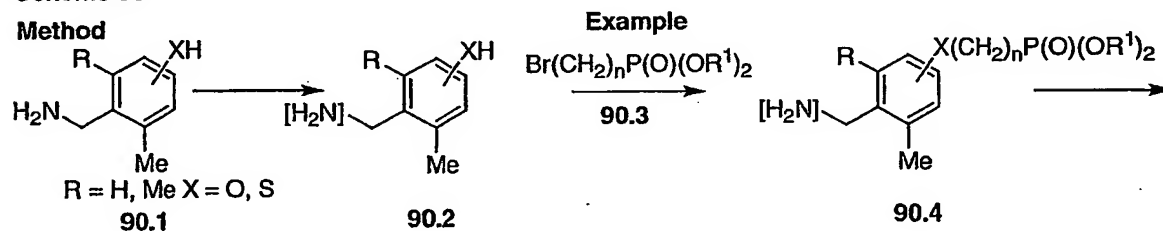
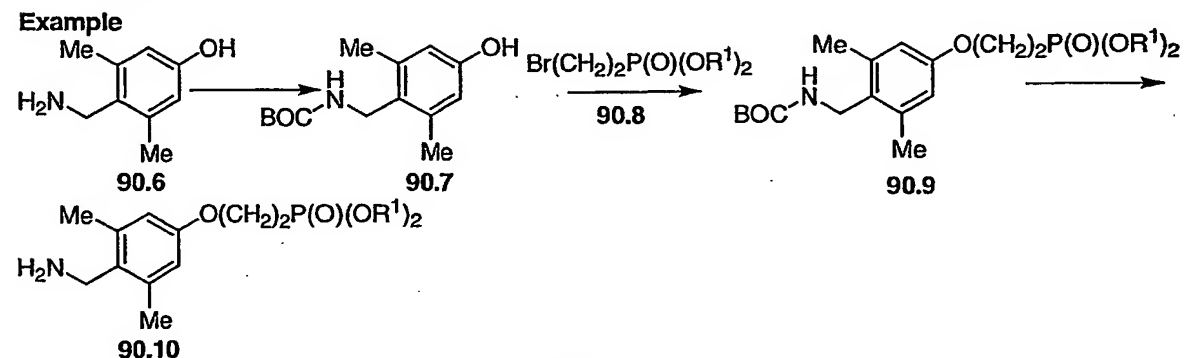
20 Using the above procedures, but employing, in place of 4-carboxy-2-methylbenzylamine 89.6, different carboxy-substituted benzylamines 89.1, and/or different aminoalkyl phosphonates 89.3, the corresponding products 89.5 are obtained.

Scheme 90 depicts the preparation of 2-methyl or 2,6-dimethylbenzylamines incorporating a
25 phosphonate moiety attached to the benzene ring by means of a heteroatom and an alkylene chain. In this procedure, the amino group of a hydroxy or mercapto-substituted methylbenzylamine 90.1 is protected to afford the derivative 90.2. This material is then reacted with a dialkyl bromoalkyl phosphonate 90.3 to yield the ether or thioether product 90.4. The reaction is conducted in a polar organic solvent such as dimethylformamide or N-
30 methylpyrrolidinone, in the presence of a base such as diazabicyclononene or cesium carbonate. The amino protecting group is then removed to afford the product 90.5.

For example, 2,6-dimethyl-4-hydroxybenzylamine **90.6**, prepared, as described above, from 2,6-dimethyl-4-hydroxybenzoic acid, the preparation of which is described in J. Org. Chem., 1985, 50, 2867, is protected to afford the BOC derivative **90.7**. The latter compound is then reacted with one molar equivalent of a dialkyl bromoethyl phosphonate **90.8**, (Aldrich) and cesium carbonate in dimethylformamide solution at 80° to give the ether **90.9**. Deprotection then afford the amine **90.10**.

Using the above procedures, but employing, in place of 4-hydroxy-2,6-dimethylbenzylamine **90.6**, different hydroxy or mercapto-substituted benzylamines **90.1**, and/or different bromoalkyl phosphonates **90.3**, the corresponding products **90.5** are obtained.

10

Scheme 89**Method****Example****Scheme 90****Method****Example**

Preparation of phosphonate-substituted decahydroquinolines 33.1.

Schemes 91 – 97 illustrate the preparation of decahydroisoquinoline derivatives 33.1 in which
5 the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc. The compounds are employed in the preparation of the intermediate phosphonate esters 9, (Schemes 33 – 36)

Scheme 91 illustrates methods for the synthesis of intermediates for the preparation of
10 decahydroquinolines with phosphonate moieties at the 6-position. Two methods for the preparation of the benzenoid intermediate 91.4 are shown.

In the first route, 2-hydroxy-6-methylphenylalanine 91.1, the preparation of which is described in J. Med. Chem., 1969, 12, 1028, is converted into the protected derivative 91.2. For example, the carboxylic acid is first transformed into the benzyl ester, and the product is
15 reacted with acetic anhydride in the presence of an organic base such as, for example, pyridine, to afford the product 91.2, in which R is benzyl. This compound is reacted with a brominating agent, for example N-bromosuccinimide, to effect benzylic bromination and yield the product 91.3. The reaction is conducted in an aprotic solvent such as, for example, ethyl acetate or carbon tetrachloride, at reflux. The brominated compound 91.3 is then treated with acid, for
20 example dilute hydrochloric acid, to effect hydrolysis and cyclization to afford the tetrahydroisoquinoline 91.4, in which R is benzyl.

Alternatively, the tetrahydroisoquinoline 91.4 can be obtained from 2-hydroxyphenylalanine 91.5, the preparation of which is described in Can. J. Bioch., 1971, 49, 877. This compound is subjected to the conditions of the Pictet-Spengler reaction, for example as described in Chem.
25 Rev., 1995, 95, 1797.

Typically, the substrate 91.5 is reacted with aqueous formaldehyde, or an equivalent such as paraformaldehyde or dimethoxymethane, in the presence of hydrochloric acid, for example as described in J. Med. Chem., 1986, 29, 784, to afford the tetrahydroisoquinoline product 91.4, in which R is H. Catalytic hydrogenation of the latter compound, using, for example, a
30 platinum catalyst, as described in J. Am. Chem. Soc., 69, 1250, 1947, or using rhodium on alumina as catalyst, as described in J. Med. Chem., 1995, 38, 4446, then gives the hydroxy-

substituted decahydroisoquinoline **91.6**. The reduction can also be performed electrochemically, as described in Trans SAEST 1984, 19, 189.

For example, the tetrahydroisoquinoline **91.4** is subjected to hydrogenation in an alcoholic solvent, in the presence of a dilute mineral acid such as hydrochloric acid, and 5% rhodium on alumina as catalyst. The hydrogenation pressure is ca. 750 psi, and the reaction is conducted at
5 ca 50°, to afford the decahydroisoquinoline **91.6**.

Protection of the carboxyl and NH groups present in **91.6** for example by conversion of the carboxylic acid into the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and conversion of the NH
10 into the N-cbz group, as described above, followed by oxidation, using, for example, pyridinium chlorochromate and the like, as described in Reagents for Organic Synthesis, by L. F. Fieser and M. Fieser, Volume 6, p. 498, affords the protected ketone **91.9**, in which R is trichloroethyl and R₁ is cbz. Reduction of the ketone, for example by the use of sodium borohydride, as described in J. Am. Chem. Soc., 88, 2811, 1966, or lithium tri-tertiary butyl
15 aluminum hydride, as described in J. Am. Chem. Soc., 80, 5372, 1958, then affords the alcohol **91.10**.

For example, the ketone is reduced by treatment with sodium borohydride in an alcoholic solvent such as isopropanol, at ambient temperature, to afford the alcohol **91.10**.

The alcohol **91.6** can be converted into the thiol **91.13** and the amine **91.14**, by means of
20 displacement reactions with suitable nucleophiles, with inversion of stereochemistry. For example, the alcohol **91.6** can be converted into an activated ester such as the trifluoromethanesulfonyl ester or the methanesulfonate ester **91.7**, by treatment with methanesulfonyl chloride and a base. The mesylate **91.7** is then treated with a sulfur nucleophile, for example potassium thioacetate, as described in Tet. Lett., 1992, 4099, or
25 sodium thiophosphate, as described in Acta Chem. Scand., 1960, 1980, to effect displacement of the mesylate, followed by mild basic hydrolysis, for example by treatment with aqueous ammonia, to afford the thiol **91.13**.

For example, the mesylate **91.7** is reacted with one molar equivalent of sodium thioacetate in a polar aprotic solvent such as, for example, dimethylformamide, at ambient temperature, to
30 afford the thioacetate **91.12**, in which R is COCH₃. The product then treated with, a mild base such as, for example, aqueous ammonia, in the presence of an organic co-solvent such as ethanol, at ambient temperature, to afford the thiol **91.13**.

The mesylate **91.7** can be treated with a nitrogen nucleophile, for example sodium phthalimide or sodium bis(trimethylsilyl)amide, as described in Comprehensive Organic Transformations, by R. C. Larock, p399, followed by deprotection as described previously, to afford the amine **91.14**.

- 5 For example, the mesylate **91.7** is reacted, as described in Angew. Chem. Int. Ed., 7, 919, 1968, with one molar equivalent of potassium phthalimide, in a dipolar aprotic solvent, such as, for example, dimethylformamide, at ambient temperature, to afford the displacement product **91.8**, in which NR^aR^b is phthalimido. Removal of the phthalimido group, for example by treatment with an alcoholic solution of hydrazine at ambient temperature, as described in J. Org. Chem., 38, 3034, 1973, then yields the amine **91.14**.

The application of the procedures described above for the conversion of the β -carbinol **91.6** to the α -thiol **91.13** and the α -amine **91.14** can also be applied to the α -carbinol **91.10**, so as to afford the β -thiol and β -amine, **91.11**.

- 15 Scheme 92 illustrates the preparation of compounds in which the phosphonate moiety is attached to the decahydroisoquinoline by means of a heteroatom and a carbon chain. In this procedure, an alcohol, thiol or amine **92.1** is reacted with a bromoalkyl phosphonate **92.2**, under the conditions described above for the preparation of the phosphonate **90.4** (Scheme 90), to afford the displacement product **92.3**. Removal of the ester group, followed by conversion of the acid to the $\text{R}^4\text{R}^5\text{N}$ amide and N-deprotection, as described herein, (Scheme 96) then yields the amine **92.8**.

- For example, the compound **92.5**, in which the carboxylic acid group is protected as the trichloroethyl ester, as described in Protective Groups in Organic Synthesis, by T. W. Greene and P.G.M. Wuts, Wiley, 1991, p. 240, and the amine is protected as the cbz group, is reacted with a dialkyl 3-bromopropylphosphonate, **92.6**, the preparation of which is described in J. Am. Chem. Soc., 2000, 122, 1554 to afford the displacement product **92.7**. Deprotection of the ester group, followed by conversion of the acid to the $\text{R}^4\text{R}^5\text{N}$ amide and N-deprotection, as described herein, (Scheme 96) then yields the amine **92.8**.

- Using the above procedures, but employing, in place of the α -thiol **92.5**, the alcohols, thiols or amines **91.6**, **91.10**, **91.11**, **91.13**, **91.14**, of either α - or β -orientation, there are obtained the corresponding products **92.4**, in which the orientation of the side chain is the same as that of the O, N or S precursors.

Scheme 93 illustrates the preparation of phosphonates linked to the decahydroisoquinoline moiety by means of a nitrogen atom and a carbon chain. The compounds are prepared by means of a reductive amination procedure, for example as described in Comprehensive

5 Organic Transformations, by R. C. Larock, p421.

In this procedure, the amines 91.14 or 91.11 are reacted with a phosphonate aldehyde 93.1, in the presence of a reducing agent, to afford the alkylated amine 93.2. Deprotection of the ester group, followed by conversion of the acid to the R^4NH amide and N-deprotection, as described herein, (Scheme 96) then yields the amine 93.3.

10 For example, the protected amino compound 91.14 is reacted with a dialkyl formylphosphonate 93.4, the preparation of which is described in US Patent 3784590, in the presence of sodium cyanoborohydride, and a polar organic solvent such as ethanolic acetic acid, as described in Org. Prep. Proc. Int., 11, 201, 1979, to give the amine phosphonate 93.5. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and
15 N-deprotection, as described herein, (Scheme 96) then yields the amine 93.6.

Using the above procedures, but employing, instead of the α -amine 91.14, the β isomer, 91.11 and/or different aldehydes 93.1, there are obtained the corresponding products 93.3, in which the orientation of the side chain is the same as that of the amine precursor.

20 Scheme 94 depicts the preparation of a decahydroisoquinoline phosphonate in which the phosphonate moiety is linked by means of a sulfur atom and a carbon chain.

In this procedure, a thiol phosphonate 94.2 is reacted with a mesylate 94.1, to effect displacement of the mesylate group with inversion of stereochemistry, to afford the thioether product 94.3. Deprotection of the ester group, followed by conversion of the acid to the

25 R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine 94.4.

For example, the protected mesylate 94.5 is reacted with an equimolar amount of a dialkyl 2-mercaptoethyl phosphonate 94.6, the preparation of which is described in Aust. J. Chem., 43, 1123, 1990. The reaction is conducted in a polar organic solvent such as ethanol, in the
30 presence of a base such as, for example, potassium carbonate, at ambient temperature, to afford the thio ether phosphonate 94.7. Deprotection of the ester group, followed by

conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine 94.8

Using the above procedures, but employing, instead of the phosphonate 94.6, different phosphonates 94.2, there are obtained the corresponding products 94.4.

5

Scheme 95 illustrates the preparation of decahydroisoquinoline phosphonates 95.4 in which the phosphonate group is linked by means of an aromatic or heteroaromatic ring. The compounds are prepared by means of a displacement reaction between hydroxy, thio or amino substituted substrates 95.1 and a bromomethyl substituted phosphonate 95.2. The reaction is performed in an aprotic solvent in the presence of a base of suitable strength, depending on the nature of the reactant 95.1. If X is S or NH, a weak organic or inorganic base such as triethylamine or potassium carbonate can be employed. If X is O, a strong base such as sodium hydride or lithium hexamethyldisilylazide is required. The displacement reaction affords the ether, thioether or amine compounds 95.3. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine 95.4.

10

15

For example, the protected alcohol 95.5 is reacted at ambient temperature with a dialkyl 3-bromomethyl phenylmethylphosphonate 95.6, the preparation of which is described above, (Scheme 80). The reaction is conducted in a dipolar aprotic solvent such as, for example, dioxan or dimethylformamide. The solution of the carbinol is treated with one equivalent of a strong base, such as, for example, lithium hexamethyldisilylazide, and to the resultant mixture is added one molar equivalent of the bromomethyl phosphonate 95.6, to afford the product 95.7. Deprotection of the ester group, followed by conversion of the acid to the R^4R^5N amide and N-deprotection, as described herein, (Scheme 96) then yields the amine 95.8.

20

25

Using the above procedures, but employing, instead of the β -carbinol 95.5, different carbinols, thiols or amines 95.1, of either α - or β -orientation, and/or different phosphonates 95.2, in place of the phosphonate 95.6, there are obtained the corresponding products 95.4 in which the orientation of the side-chain is the same as that of the starting material 95.1.

30

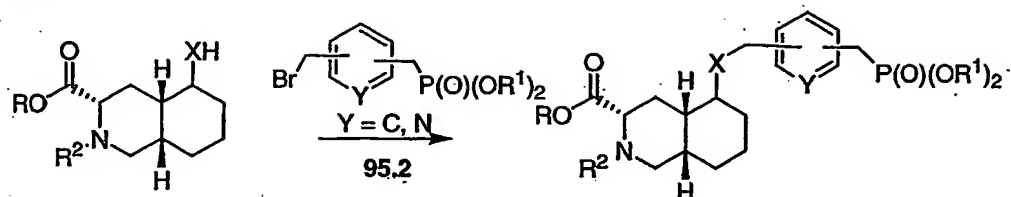
Schemes 92-95 illustrate the preparation of decahydroisoquinoline esters incorporating a phosphonate group linked to the decahydroisoquinoline nucleus.

Scheme 96 illustrates the conversion of the latter group of compounds 96.1 (in which the group B is link-P(O)(OR¹)₂ or optionally protected precursor substituents thereto, such as, for example, OH, SH, NH₂) to the corresponding R⁴R⁵N amides 96.5.

5 As shown in Scheme 96, the ester compounds 96.1 are deprotected to form the corresponding carboxylic acids 96.2. The methods employed for the deprotection are chosen based on the nature of the protecting group R, the nature of the N-protecting group R², and the nature of the substituent at the 6-position. For example, if R is trichloroethyl, the ester group is removed by treatment with zinc in acetic acid, as described in J. Am. Chem. Soc., 88, 852, 1966.

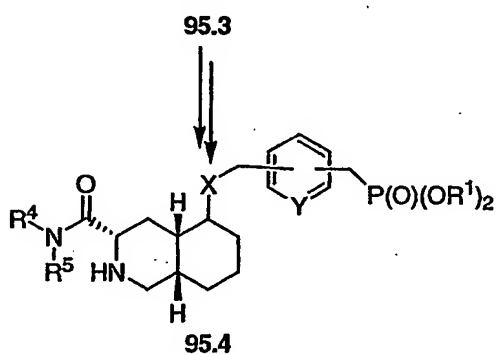
10 Conversion of the carboxylic acid 96.2 to the R⁴R⁵N amide 96.4 is then accomplished by reaction of the carboxylic acid, or an activated derivative thereof, with the amine R⁴R⁵NH 96.3 to afford the amide 96.4, using the conditions described above for the preparation of the amide 1.6. Deprotection of the NR² group, as described above, then affords the free amine 96.5.

Scheme 95
Method

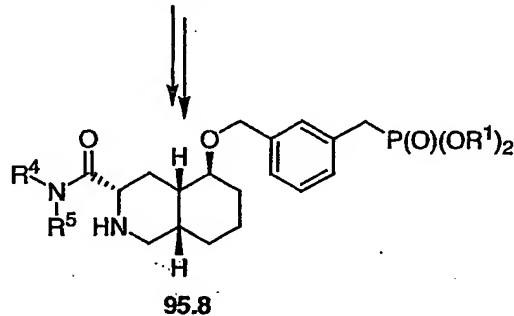
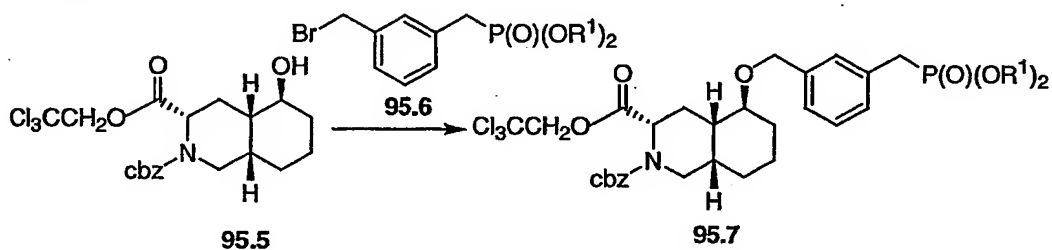


95.1 X = O, S, NH

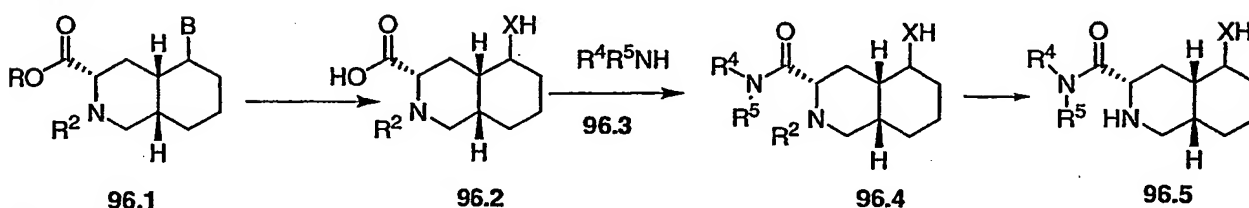
R² = protecting group



Example



Scheme 96
Method



R² = protecting group

Preparation of the phosphonate-containing tert. butylamides 37.1.

Scheme 97 illustrates the preparation of the amides 37.1 in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters 10 (Schemes 37 – 40). In this procedure, the BOC-protected decahydroisoquinoline carboxylic acid 97.1 is reacted with the tert. butylamine derivative 25.1, in which the substituent A is the group link- $P(O)(OR^1)_2$, or a precursor group thereto, such as [OH], [SH], Br, etc, to afford the amide 97.2. The reaction is conducted as described above for the preparation of the amides 1.3 and 1.6. The BOC protecting group is then removed to yield the amine 37.1.

Preparation of the phosphonate-containing thiazolidines 21.1.

Schemes 98 - 101 illustrate the preparation of the thiazolidine derivatives 37.1, in which the substituent A is either the group link $P(O)(OR^1)_2$ or a precursor thereto, such as [OH], [SH], Br etc, which are employed in the preparation of the intermediate phosphonate esters 6. The preparation of the penicillamine analogs 98.5 in which R is alkyl is described in J. Org. Chem., 1986, 51, 5153 and in J. Labelled. Comp. Radiochem., 1987, 24, 1265. The conversion of the penicillamine analogs 98.5 into the corresponding thiazolidines 98.7 is described in J. Med. Chem., 1999, 42, 1789 and in J. Med. Chem., 1989, 32, 466. The above-cited procedures, and their use to afford analogs of the thiazolidines 98.7 are shown in Scheme 98.

In this procedure, a methyl ketone 98.2 is reacted with methyl isocyanoacetate 98.1 to afford the aminoacrylate product 98.3. The condensation reaction is conducted in the presence of a base such as butyllithium or sodium hydride, in a solvent such as tetrahydrofuran at from -80° to 0° , to afford after treatment with aqueous ammonium chloride the N-formyl acrylate ester 98.3. The latter compound is then reacted with phosphorus pentasulfide or Lawessons reagent and the like to yield the thiazoline derivative 98.4. The reaction is performed in an aprotic solvent such as benzene, for example as described in J. Org. Chem., 1986, 51, 5153. The thiazoline product 98.4 is then treated with dilute acid, for example dilute hydrochloric acid, to produce the aminothiols 98.5. This compound is reacted with aqueous formaldehyde at pH 5, for example as described in J. Med. Chem., 1999, 42, 1789, to prepare the thiazolidine 98.6. The product is then converted, as described previously, into the BOC-protected analog 98.7.

Some examples of the use of the reactions of Scheme 98 for the preparation of functionally substituted thiazolidines 98.7 are shown below.

Scheme 98, Example 1 illustrates the preparation of the BOC-protected hydroxymethyl thiazolidine 98.11. In this procedure, methyl isocyanoacetate 98.1 is reacted with
5 hydroxyacetone 98.8 in the presence of a base such as sodium hydride, to yield the aminoacrylate derivative 98.9. The product is then reacted with phosphorus pentasulfide, as described above, to prepare the thiazoline 98.10. The latter compound is then converted, as described above, into the thiazolidine derivative 98.11.

Scheme 98, Example 2, depicts the preparation of bromophenyl-substituted thiazolidines
10 98.14. In this reaction sequence, methyl isocyanoacetate 98.1 is condensed, as described above, with a bromoacetophenone 98.12 to give the aminocinnamate derivative 98.13. The latter compound is then transformed, as described above, into the thiazolidine derivative 98.14.

Scheme 98, Example 3 depicts the preparation of the BOC-protected
15 thiazolidine-5-carboxylic acid 98.18. In this procedure, methyl isocyanoacetate 98.1 is reacted, as described above, with trichloroethyl pyruvate 98.15 to afford the aminoacrylate derivative 98.16. This compound is then transformed, as described above, into the thiazolidine diester 98.17. The trichloroethyl ester is then cleaved, for example by treatment with zinc in aqueous tetrahydrofuran at pH 4.2, as described in J. Am. Chem. Soc., 88, 852, 1966, to afford the 5-
20 carboxylic acid 98.18.

Scheme 98, Example 4, depicts the preparation of the BOC-protected thiazolidine-4-carboxylic acid incorporating a phosphonate moiety. In this procedure, methyl isocyanoacetate 98.1 is condensed, as described above, with a dialkyl 2-oxopropyl phosphonate 98.19, (Aldrich); the product 98.20 is then transformed, as described above, into the corresponding
25 4-carbomethoxythiazolidine. Hydrolysis of the methyl ester, for example by the use of one equivalent of lithium hydroxide in aqueous tetrahydrofuran, then yields the carboxylic acid 98.21.

Scheme 99 illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids
30 incorporating a phosphonate group attached by means of an oxygen atom and an alkylene chain. In this procedure, the hydroxymethyl thiazolidine 98.11 is reacted with a dialkyl bromoalkyl phosphonate 99.1 to afford the ether product 99.2. The hydroxymethyl substrate

98.11 is treated in dimethylformamide solution with a strong base such as sodium hydride or lithium hexamethyldisilylazide, and an equimolar amount of the bromo compound **99.1** is added. The product **99.2** is then treated with aqueous base, as described above, to effect hydrolysis of the methyl ester to yield the carboxylic acid **99.3**.

- 5 For example, the hydroxymethyl thiazolidine **98.11** is reacted with sodium hydride and a dialkyl bromoethyl phosphonate **99.4** (Aldrich) in dimethylformamide at 70°, to produce the phosphonate product **99.5**. Hydrolysis of the methyl ester then affords the carboxylic acid **99.6**.

Using the above procedures, but employing, in place of the dialkyl bromoethyl phosphonate
10 **99.4**, different bromoalkyl phosphonates **99.1**, the corresponding products **99.3** are obtained.

Scheme **100** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of a phenyl group. In this procedure, a bromophenyl-substituted thiazolidine **98.14** is coupled, as described above (Scheme **46**) in the
15 presence of a palladium catalyst, with a dialkyl phosphite **100.1**, to produce the phenylphosphonate derivative **100.2**. The methyl ester is then hydrolyzed to afford the carboxylic acid **100.3**.

For example, the BOC-protected 5-(4-bromophenyl)thiazolidine **100.4** is coupled with a dialkyl phosphite **100.1** to yield the product **100.5**, which upon hydrolysis affords the
20 carboxylic acid **100.6**.

Using the above procedures, but employing, in place of the 4-bromophenyl thiazolidine **100.4**, different bromophenyl thiazolidines **98.14**, the corresponding products **100.3** are obtained.

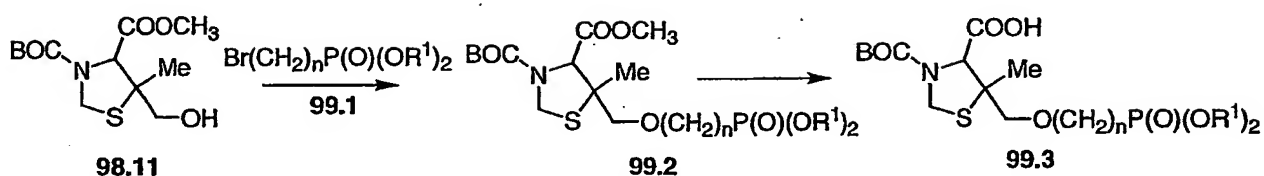
Scheme **101** illustrates the preparation of BOC-protected thiazolidine-4-carboxylic acids incorporating a phosphonate group attached by means of an amide linkage. In this procedure,
25 a thiazolidine-5-carboxylic acid **98.18** is reacted with a dialkyl aminoalkyl phosphonate **101.1** to produce the amide **101.2**. The reaction is conducted as described above for the preparation of the amides **1.3** and **1.6**. The methyl ester is then hydrolyzed to afford the carboxylic acid **101.3**.

For example, the carboxylic acid **98.18** is reacted in tetrahydrofuran solution with an
30 equimolar amount of a dialkyl aminopropyl phosphonate **101.4** (Acros) and dicyclohexylcarbodiimide, to afford the amide **101.5**. The methyl ester is then hydrolyzed to afford the carboxylic acid **101.6**.

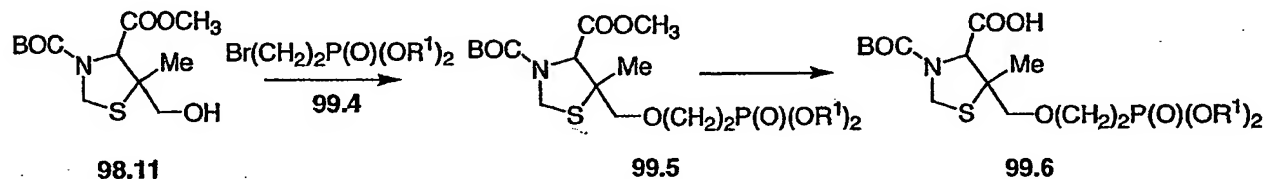
Using the above procedures, but employing, in place of the dialkyl aminopropyl phosphonate **101.4**, different aminoalkyl phosphonates **101.1**, the corresponding products **101.3** are obtained.

Scheme 99

Method

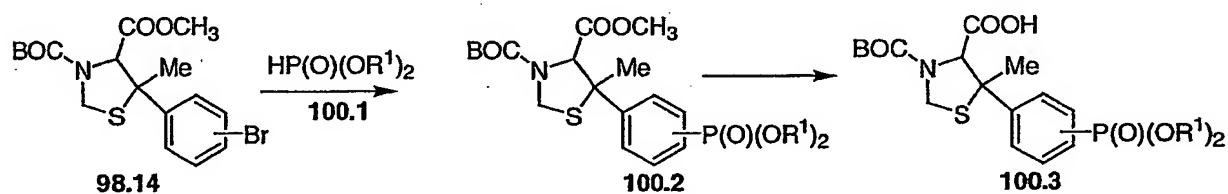


Example

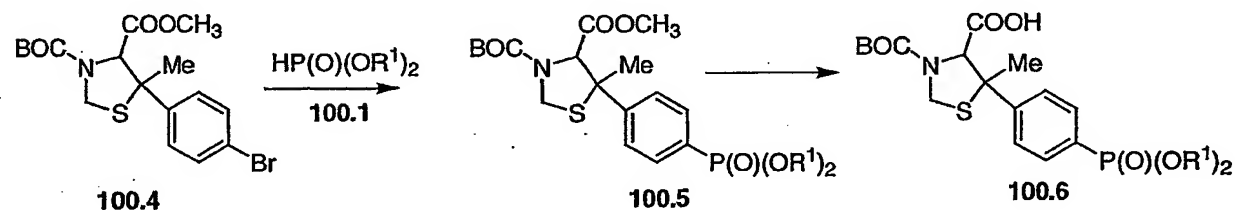


Scheme 100

Method

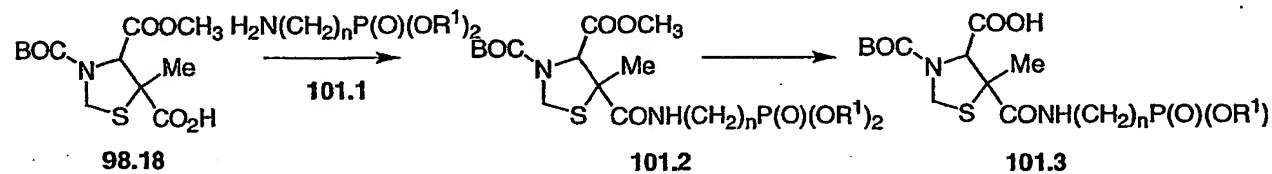


Example

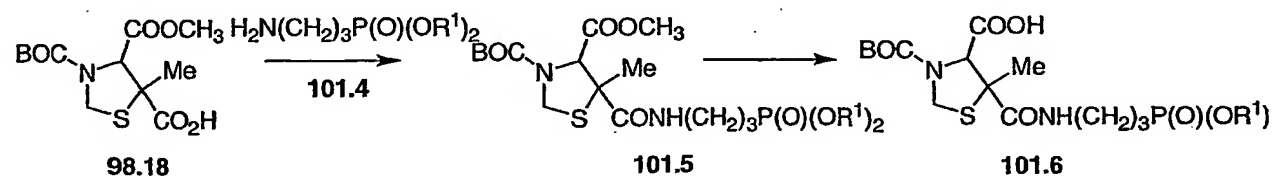


Scheme 101

Method



Example



Preparation of carbamates.

The phosphonate esters 5 - 12 in which the R⁸CO groups are formally derived from the
5 carboxylic acids C38 - C49 (Chart 2c) contain a carbamate linkage. The preparation of
carbamates is described in Comprehensive Organic Functional Group Transformations, A. R.
Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group
Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff.
Scheme 102 illustrates various methods by which the carbamate linkage can be synthesized. As
10 shown in Scheme 102, in the general reaction generating carbamates, a carbinol 102.1, is
converted into the activated derivative 102.2 in which Lv is a leaving group such as halo,
imidazolyl, benztriazolyl and the like, as described herein. The activated derivative 102.2 is
then reacted with an amine 102.3, to afford the carbamate product 102.4. Examples 1 - 7 in
Scheme 102 depict methods by which the general reaction can be effected. Examples 8 - 10
15 illustrate alternative methods for the preparation of carbamates.
Scheme 102, Example 1 illustrates the preparation of carbamates employing a chloroformyl
derivative of the carbinol 102.5. In this procedure, the carbinol 102.5 is reacted with
phosgene, in an inert solvent such as toluene, at about 0°, as described in Org. Syn. Coll. Vol.
3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as
20 described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate 102.6. The latter
compound is then reacted with the amine component 102.3, in the presence of an organic or
inorganic base, to afford the carbamate 102.7. For example, the chloroformyl compound 102.6
is reacted with the amine 102.3 in a water-miscible solvent such as tetrahydrofuran, in the
presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to
25 yield the carbamate 102.7. Alternatively, the reaction is performed in dichloromethane in the
presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.
Scheme 102, Example 2 depicts the reaction of the chloroformate compound 102.6 with
imidazole to produce the imidazolide 102.8. The imidazolide product is then reacted with the
amine 102.3 to yield the carbamate 102.7. The preparation of the imidazolide is performed in
30 an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is
conducted in a similar solvent at ambient temperature, optionally in the presence of a base
such as dimethylaminopyridine, as described in J. Med. Chem., 1989, 32, 357.

Scheme 102 Example 3, depicts the reaction of the chloroformate 102.6 with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester 102.10. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds 102.19 - 102.24 shown in Scheme 102, and similar compounds. For example, if the component R"OH is hydroxybenztriazole 102.19, N-hydroxysuccinimide 102.20, or pentachlorophenol, 102.21, the mixed carbonate 102.10 is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in Can. J. Chem., 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol 102.22 or 2-hydroxypyridine 102.23 can be performed in an ethereal solvent in the presence of triethylamine, as described in Syn., 1986, 303, and Chem. Ber. 118, 468, 1985.

Scheme 102 Example 4 illustrates the preparation of carbamates in which an alkoxycarbonylimidazole 102.8 is employed. In this procedure, a carbinol 102.5 is reacted with an equimolar amount of carbonyl diimidazole 102.11 to prepare the intermediate 102.8. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole 102.8 is then reacted with an equimolar amount of the amine RNH₂ to afford the carbamate 102.7. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in Tet. Lett., 42, 2001, 5227, to afford the carbamate 102.7.

Scheme 102, Example 5 illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole 102.13. In this procedure, a carbinol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride 102.12, to afford the alkoxycarbonyl product 102.13. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in Syn., 1977, 704. The product is then reacted with the amine RNH₂ to afford the carbamate 102.7. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80° as described in Syn., 1977, 704.

Scheme 102, Example 6 illustrates the preparation of carbamates in which a carbonate (R"O)₂CO, 102.14, is reacted with a carbinol 102.5 to afford the intermediate alkoxycarbonyl intermediate 102.15. The latter reagent is then reacted with the amine RNH₂ to afford the carbamate 102.7. The procedure in which the reagent 102.15 is derived from

hydroxybenztriazole **102.19** is described in Synthesis, 1993, 908; the procedure in which the reagent **102.15** is derived from N-hydroxysuccinimide **102.20** is described in Tet. Lett., 1992, 2781; the procedure in which the reagent **102.15** is derived from 2-hydroxypyridine **102.23** is described in Tet. Lett., 1991, 4251; the procedure in which the reagent **102.15** is derived from 4-nitrophenol **102.24** is described in Syn. 1993, 103. The reaction between equimolar amounts of the carbinol ROH and the carbonate **102.14** is conducted in an inert organic solvent at ambient temperature.

Scheme **102**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **102.16**. In this procedure, an alkyl chloroformate **102.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **102.16**. The latter compound is then reacted with an equimolar amount of the amine RNH_2 to afford the carbamate **102.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in Syn., 1982, 404.

Scheme **102**, Example **8** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and the chloroformyl derivative of an amine **102.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **102.7**.

Scheme **102**, Example **9** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an isocyanate **102.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **102.7**.

Scheme **102**, Example **10** illustrates the preparation of carbamates by means of the reaction between a carbinol ROH and an amine RNH_2 . In this procedure, which is described in Chem. Lett. 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **102.7**.

Interconversions of the phosphonates R-link-P(O)(OR¹)₂, R-link-P(O)(OR¹)(OH) and R-link-P(O)(OH)₂.

Schemes 1 - 102 described the preparations of phosphonate esters of the general structure R-link-P(O)(OR¹)₂, in which the groups R¹, the structures of which are defined in Chart 1, may

5 be the same or different. The R¹ groups attached to a phosphonate esters 1 - 12, or to precursors thereto, may be changed using established chemical transformations. The interconversions reactions of phosphonates are illustrated in Scheme 103. The group R in Scheme 103 represents the substructure to which the substituent link-P(O)(OR¹)₂ is attached, either in the compounds 1 - 12 or in precursors thereto. The R¹ group may be changed, using
10 the procedures described below, either in the precursor compounds, or in the esters 1 - 12.

The methods employed for a given phosphonate transformation depend on the nature of the substituent R¹. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

The conversion of a phosphonate diester 103.1 into the corresponding phosphonate monoester
15 103.2 (Scheme 103, Reaction 1) can be accomplished by a number of methods. For example, the ester 103.1 in which R¹ is an aralkyl group such as benzyl, can be converted into the monoester compound 103.2 by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in J. Org. Chem., 1995, 60, 2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about
20 110°. The conversion of the diester 103.1 in which R¹ is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester 103.2 can be effected by treatment of the ester 103.1 with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters 103.1 in which one of the groups R¹ is aralkyl, such as benzyl, and the other is alkyl, can be converted into the monoesters 103.2 in which R¹
25 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R¹ are alkenyl, such as allyl, can be converted into the monoester 103.2 in which R¹ is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described
30 in J. Org. Chem., 38, 3224, 1973 for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **103.1** or a phosphonate monoester **103.2** into the corresponding phosphonic acid **103.3** (Scheme **103**, Reactions **2** and **3**) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in J. Chem. Soc., Chem. Comm., 739, 1979. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **103.2** in which R^1 is aralkyl such as benzyl, can be converted into the corresponding phosphonic acid **103.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxan. A phosphonate monoester **103.2** in which R^1 is alkenyl such as, for example, allyl, can be converted into the phosphonic acid **103.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in Helv. Chim. Acta., 68, 618, 1985. Palladium catalyzed hydrogenolysis of phosphonate esters **103.1** in which R^1 is benzyl is described in J. Org. Chem., 24, 434, 1959. Platinum-catalyzed hydrogenolysis of phosphonate esters **103.1** in which R^1 is phenyl is described in J. Am. Chem. Soc., 78, 2336, 1956.

The conversion of a phosphonate monoester **103.2** into a phosphonate diester **103.1** (Scheme **103**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl can be effected by a number of reactions in which the substrate **103.2** is reacted with a hydroxy compound R^1OH , in the presence of a coupling agent. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **103.2** to the diester **103.1** can be effected by the use of the Mitsunobu reaction, as described above (Scheme **47**). The substrate is reacted with the hydroxy compound R^1OH , in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **103.2** can be transformed into the phosphonate diester **103.1**, in

which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br , in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester can be transformed into the

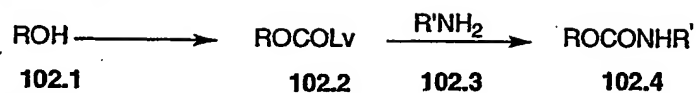
- 5 phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **103.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH , in the presence of a base such as
- 10 triethylamine, to afford the phosphonate diester **103.1**.

A phosphonic acid $R\text{-link-P}(O)(OH)_2$ can be transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme 103, Reaction 5) by means of the methods described above of for the preparation of the phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **103.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed.

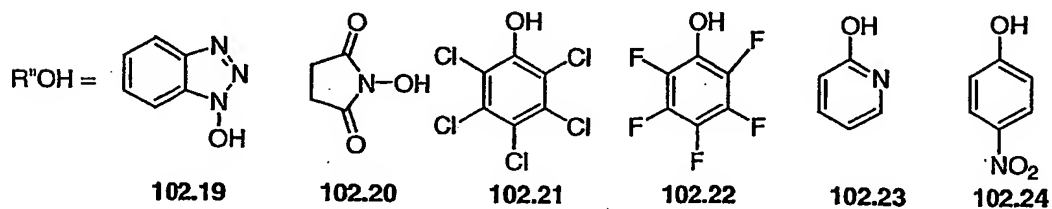
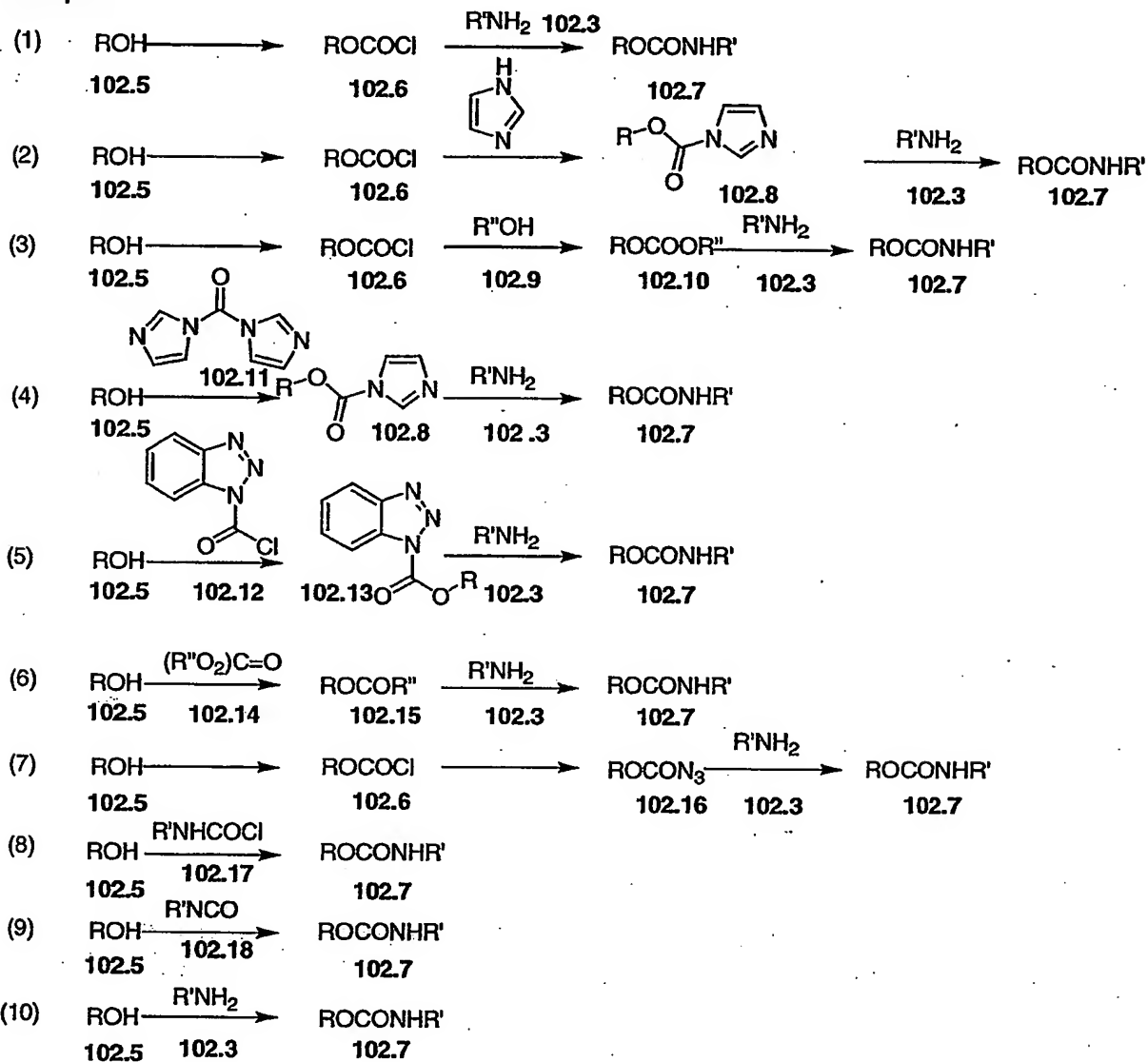
- 15 A phosphonic acid $R\text{-link-P}(O)(OH)_2$ **103.3** can be transformed into a phosphonate diester $R\text{-link-P}(O)(OR^1)_2$ **103.1** (Scheme 103, Reaction 6) by a coupling reaction with the hydroxy compound R^1OH , in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in
- 20 which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70° . Alternatively, phosphonic acids **103.3** can be transformed into phosphonic esters **103.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as
- 25 cesium carbonate, to afford the phosphonic ester **103.1**.

Scheme 102

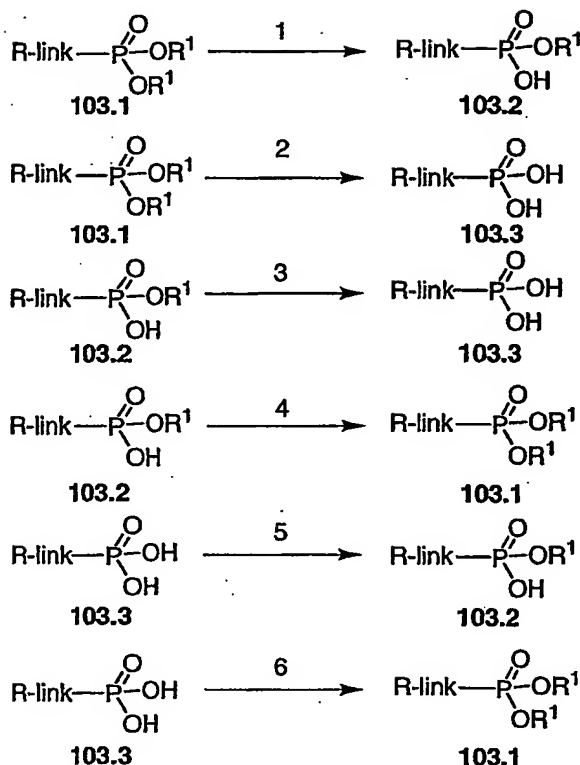
General reaction



Examples



Scheme 103



General applicability of methods for introduction of phosphonate substituents.

- The procedures described herein for the introduction of phosphonate moieties (Schemes 45 - 101) are, with appropriate modifications known to one skilled in the art, transferable to
- 5 different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups into hydroxymethyl benzoic acids (Schemes 45 - 52) are applicable to the introduction of phosphonate moieties into the dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, and the methods described herein for the introduction of phosphonate moieties into the
 - 10 dimethoxyphenol, quinoline, phenylalanine, thiophenol, tert. butylamine, benzylamine, decahydroisoquinoline or thiazolidine substrates, (Schemes 53 - 101) are applicable to the introduction of phosphonate moieties into carbinol substrates.

- Preparation of phosphonate intermediates 11 and 12 with phosphonate moieties
- 15 incorporated into the groups R^8CO and $\text{R}^{10}\text{R}^{11}\text{N}$.

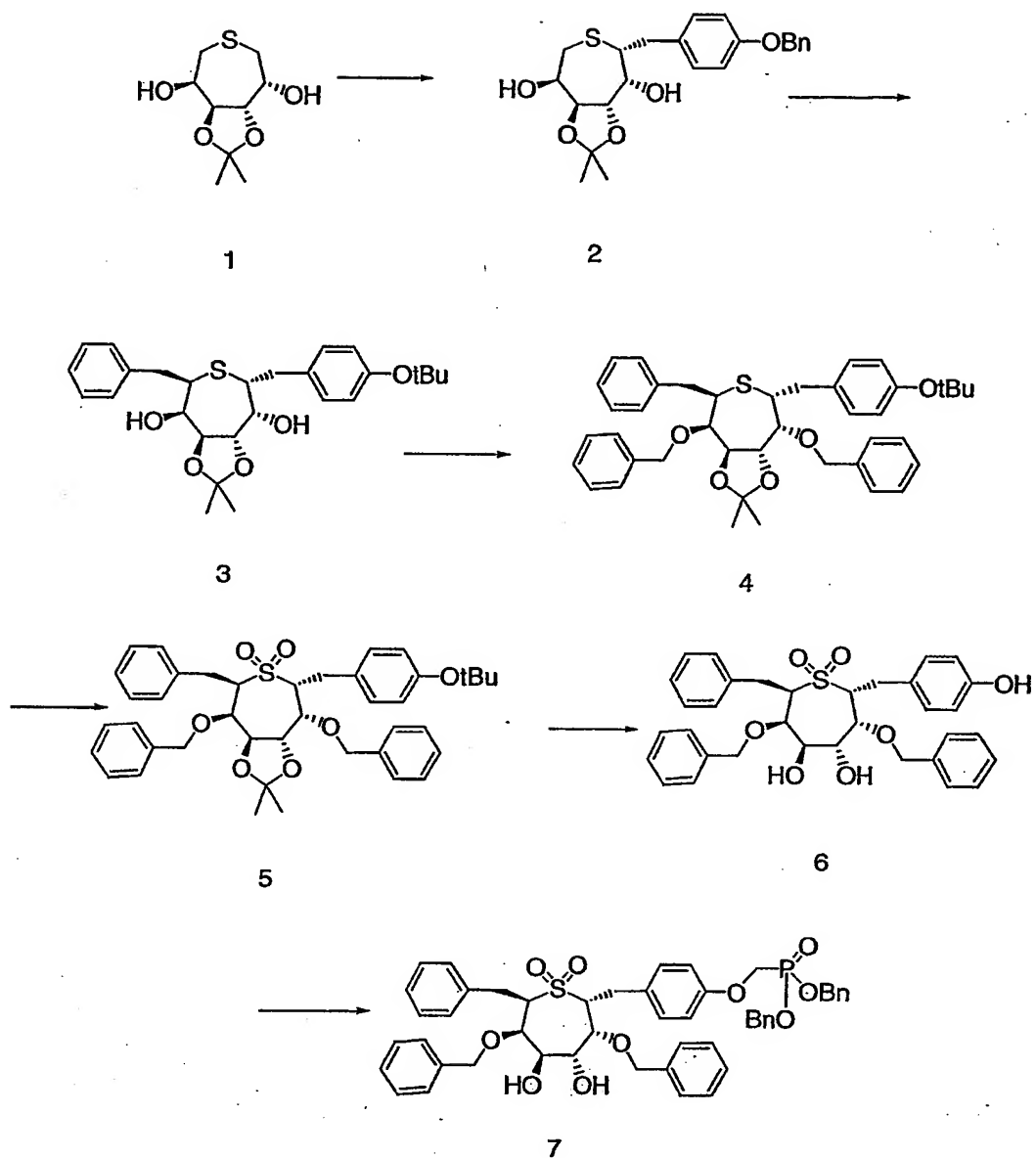
The chemical transformations described in Schemes 1 - 103 illustrate the preparation of compounds 1 -10 in which the phosphonate ester moiety is attached to the benzoic acid moiety, (Schemes 46 - 52), the dimethylphenol moiety (Schemes 53 - 56), the quinoline
5 carboxamide moiety (Schemes 57 - 61), the 5-hydroxyisoquinoline moiety (Schemes 62 - 66), the phenylalanine moiety (Schemes 67 - 71), the thiophenol moiety, (Schemes 72 - 83), the tert. butylamine moiety, (Schemes 84 - 87), the benzylamine moiety, (Schemes 88 - 90), the decahydroisoquinoline moiety, (Schemes 91 - 97) or the thiazolidine moiety, (Schemes 98 - 101). The various chemical methods employed for the preparation of phosphonate groups can,
10 with appropriate modifications known to those skilled in the art, be applied to the introduction of a phosphonate ester group into the compounds $R^8\text{COOH}$ and $R^{10}R^{11}\text{NH}$, as defined in Charts 3a, 3b, 3c and 4. The resultant phosphonate-containing analogs, designated as $R^{8a}\text{COOH}$ and $R^{10a}R^{11a}\text{NH}$ can then, using the procedures described above, be employed in the preparation of the compounds 11 and 12. The procedures required for the utilization of the
15 phosphonate-containing analogs $R^{8a}\text{COOH}$ and $R^{10a}R^{11a}\text{NH}$ are the same as those described above for the utilization of the $R^8\text{COOH}$ and $R^{10}R^{11}\text{NH}$ reactants.

Cyclic carbonyl phosphonate protease inhibitors (CCPPI)

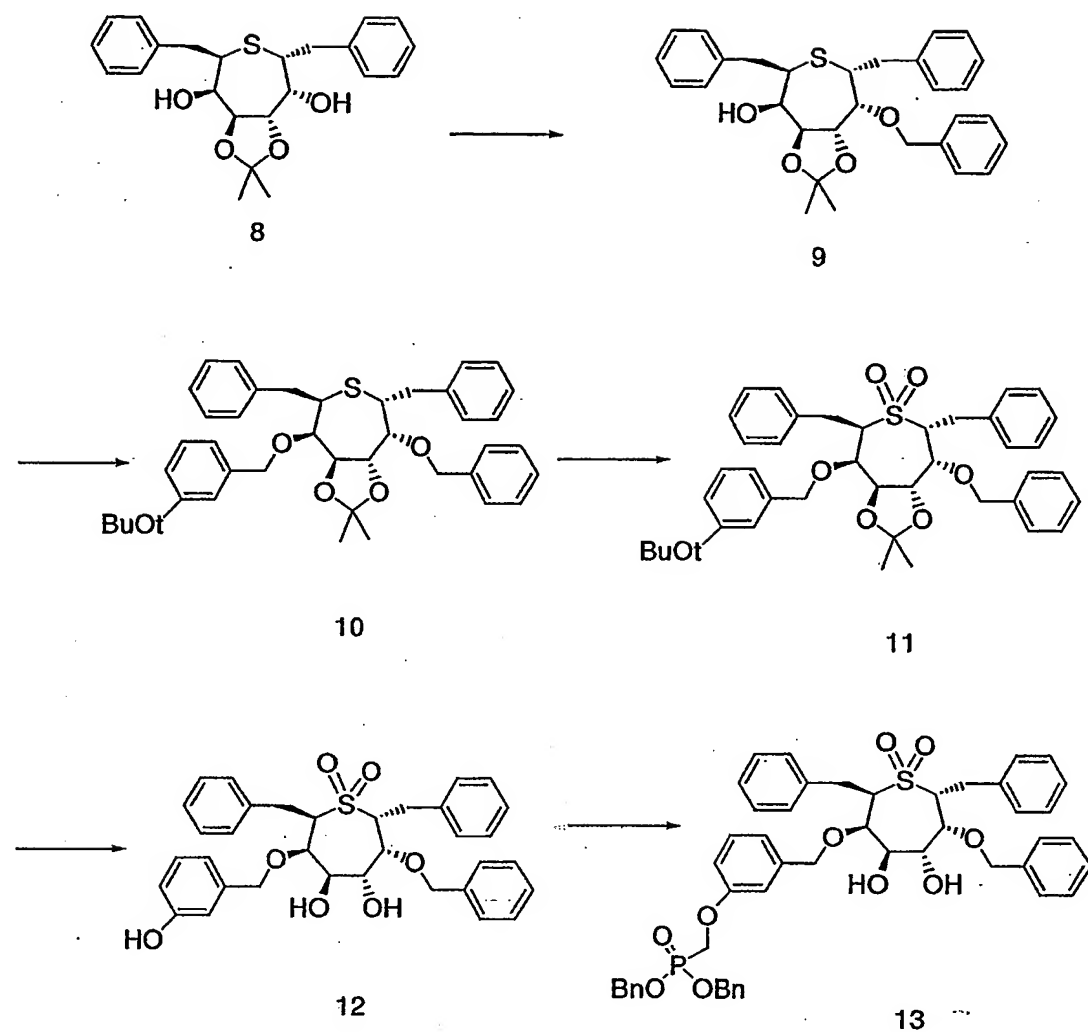
20 Scheme Section B

Schemes 1 and 2 are described below in the Examples.

Scheme 1



Scheme 2



Example Section B**Example 1**

Scheme 1 : Example, [4-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-2-ylmethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester (7)

The cyclic sulfide **1** is prepared according to the procedures reported by Kim et al. (J. Med. Chem. 1996, 39, 3431-3434) and Bischofberger (WO96/14314, Gilead Sciences). Treatment of the sulfide **1** with 4-benzyloxybenzaldehyde affords the benzyl ether **2** (J. Med. Chem. 1996, 39, 3431-3434). A second alkylation with benzaldehyde gives **3** which is subsequently treated with excess benzylbromide to afford the full substituted product **4**. Ozone is used to convert the sulfide to the sulfone **5** (J. Med. Chem. 1996, 39, 3431-3434). Sulfone **5** is treated with TFA to give the phenol **6** which upon alkylation with trifluoro-methanesulfonic acid bis-benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) gives the dibenzyl phosphonate **7**.

The meta analog, [3-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-2-ylmethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester and ortho analog, [2-(7-Benzyl-3,6-bis-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-2-ylmethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester are prepared using Scheme 1 except 4-benzyloxybenzaldehyde is replaced with 3-benzyloxybenzaldehyde and 2-benzyloxybenzaldehyde respectively.

Example 2

Scheme 2 : Example, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-3-ylomethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester (13).

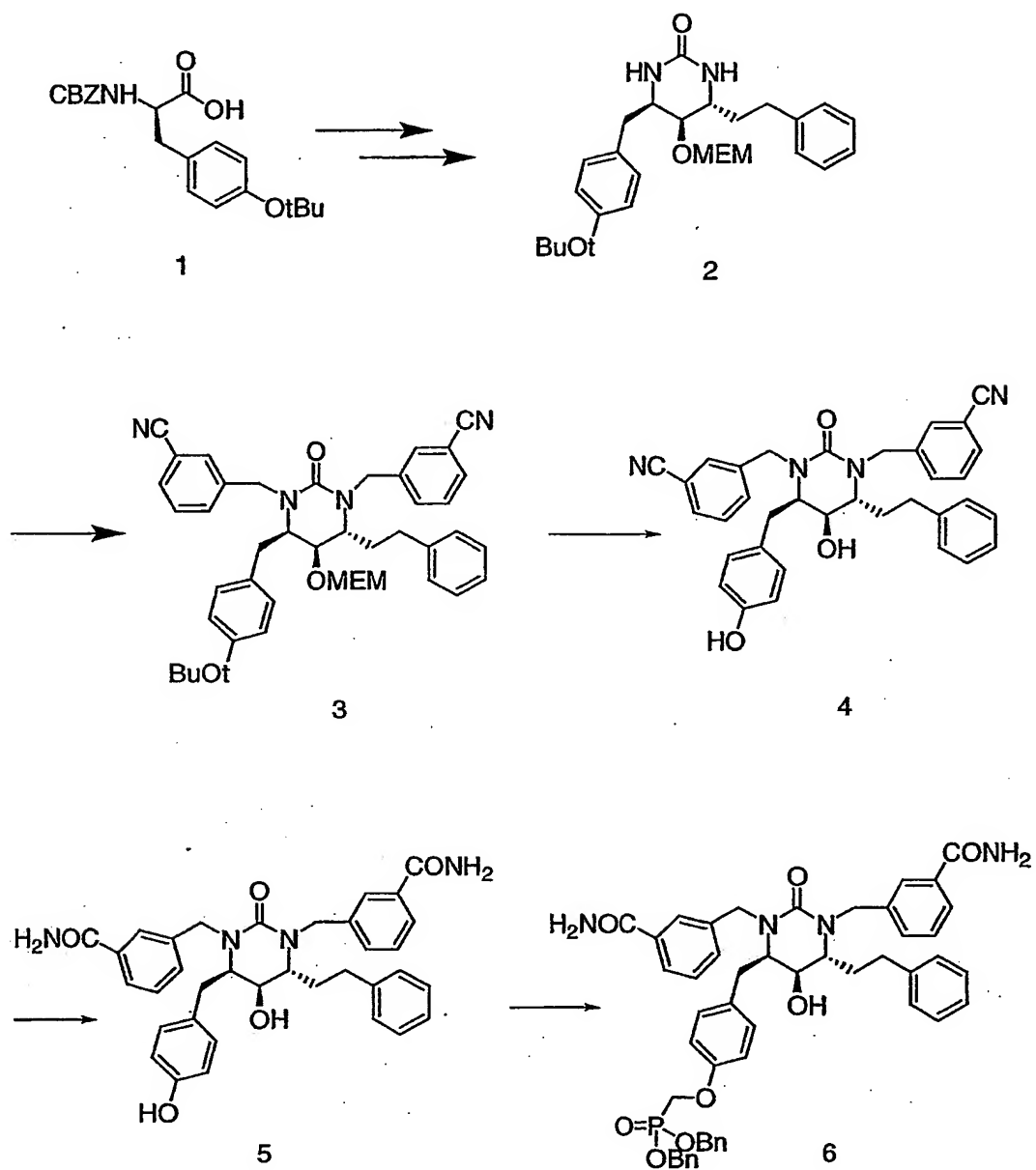
The sulfide **8** is prepared according to the procedure of Kim et al. (J. Med. Chem. 1996, 39, 3431-3434) and is then treated with benzyl bromide in the presence of sodium hydride to give the benzyl ether **9**. A second treatment with 3-t-butyloxybenzylchloride in the presence of sodium hydride affords the benzyl ether **10**. Ozone treatment of the benzyl ether **10** gives the sulfone **11**. (J. Med. Chem. 1996, 39, 3431-3434) which is then treated with TFA to give the phenol **12** (Green). Phenol **12** is treated with trifluoro-methanesulfonic acid bis-

benzyloxy-phosphorylmethyl ester in the presence of base (e.g. cesium carbonate) to give the dibenzyl phosphonate 13.

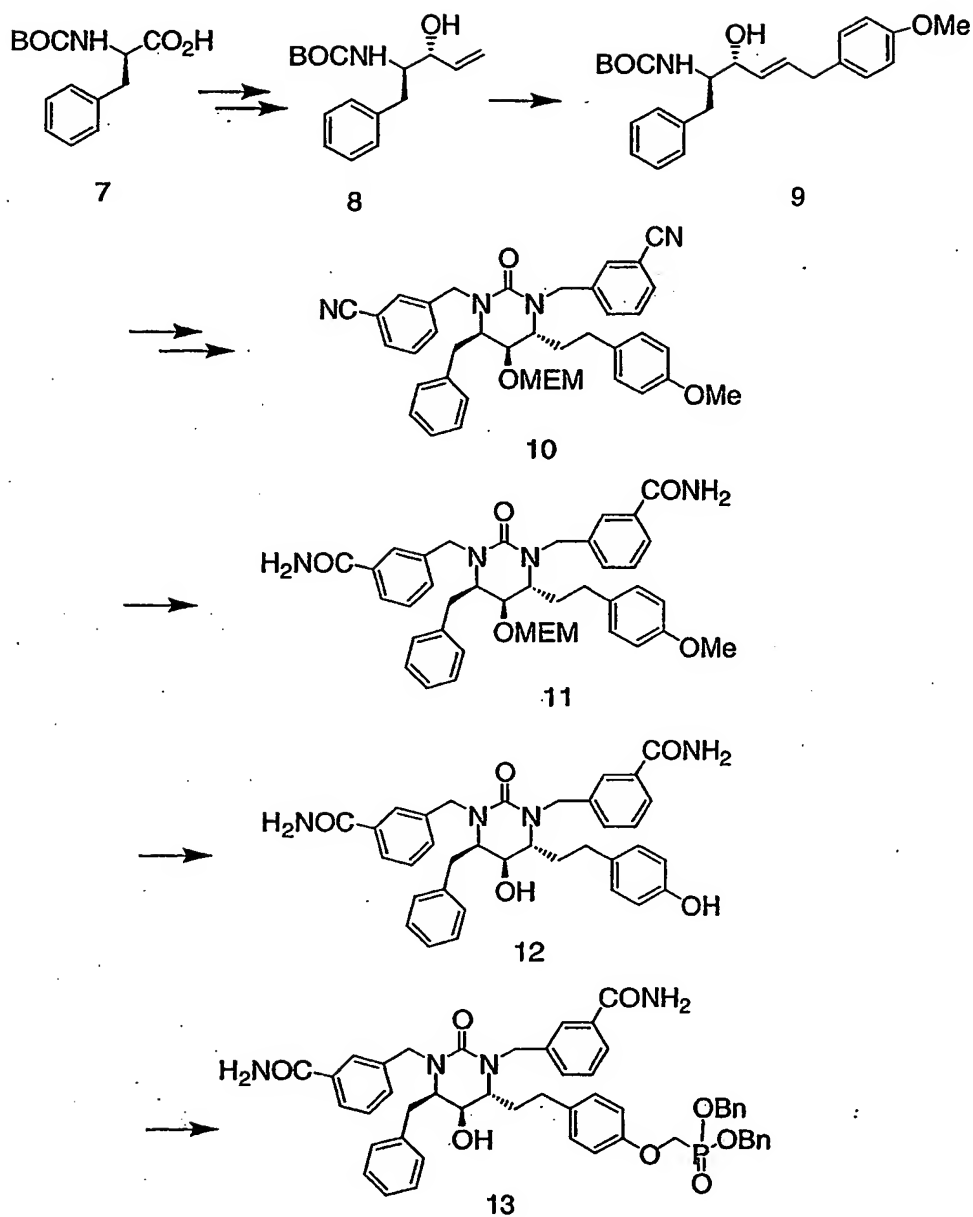
The para analog, [3-(2,7-Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-3-yloxymethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester, and ortho analog, [3-(2,7-
5 Dibenzyl-6-benzyloxy-4,5-dihydroxy-1,1-dioxo-11 β -thiepan-3-yloxymethyl)-phenoxy-methyl]-phosphonic acid dibenzyl ester, are prepared using the same procedures found in Scheme 2 except utilizing the 4-t-butyloxybenzylchloride and 2-t-butyloxybenzylchloride instead of 3-t-butyloxybenzylchloride. The benzylchlorides are prepared from the corresponding
commercially available benzylalcohols by treatment with thionyl chloride (*Jour. Chem. Soc.*
10 (1956), 2455-2461).

Scheme Section C

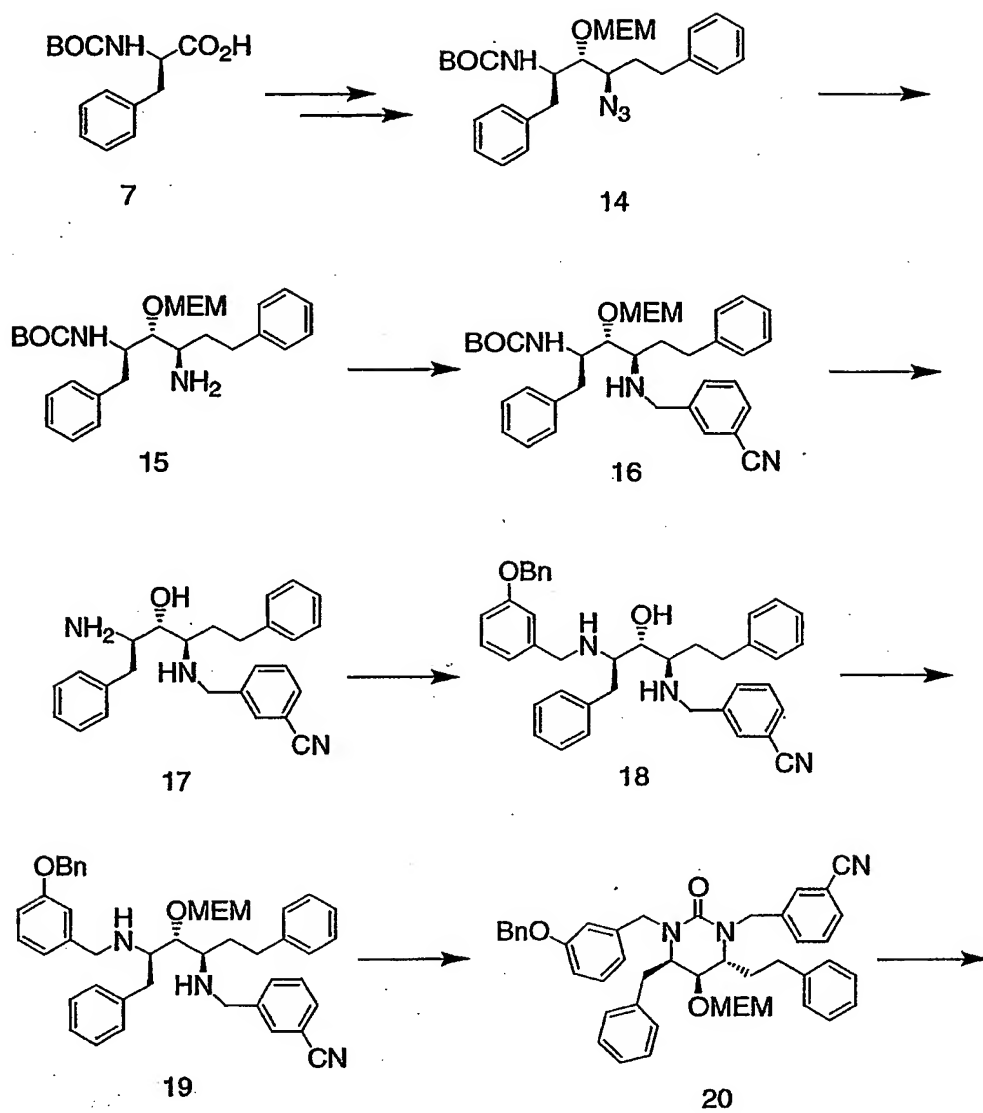
Schemes 1-4 are described in the Examples.

Scheme 1

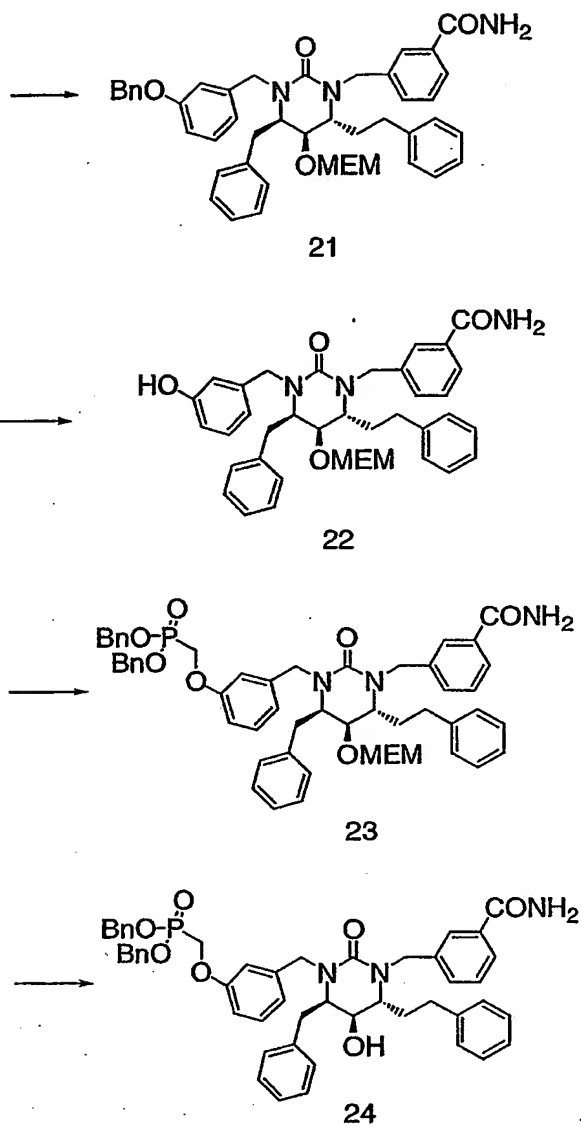
Scheme 2



Scheme 3



Scheme 3



Scheme 4

